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Uterine carcinosarcoma, leiomyosarcoma and endometrial stromal sarcoma
Epidemiological, clinical and prognostic aspects

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ACADEMIC DISSERTATION

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To Rosa, Reetta and Timo

TABLE OF CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals

I Koivisto-Korander R, Martinsen J.I, Weiderpass E, Leminen A, Pukkala E. Incidence of uterine leiomyosarcoma and endometrial stromal sarcoma in Nordic countries: results from NORDCAN and NOCCA databases. Maturitas. May 2012;72(1):56-60.

II Koivisto-Korander R, Butzow R, Koivisto A-M, Leminen A. Clinical outcome and prognostic factors in 100 cases of uterine sarcoma: experience in Helsinki University Central Hospital 1990–2001. Gynecol Oncol. 2008 Oct;111(1):74-81.

III Koivisto-Korander R, Butzow R, Koivisto A-M, Leminen A. Immunohistochemical studies on uterine carcinosarcoma, leiomyosarcoma and endometrial stromal sarcoma: expression and prognostic importance of ten different markers. Tumor Biol. 2011 Jun;32(3):451-9.

IV Koivisto-Korander R, Scélo G, Ferro G, Mellemkjaer L, Hemminki K, Weiderpass E, Tamaro S, Pompe-Kirn V, Tracey E, Brewster DH, Kliewer EV, Tonita JM, Kee-Seng C, Jonasson JG, Martos G, Brennan P, Straif K, Pukkala E. Second primary malignancies among women with uterine sarcoma. Gynecol Oncol. 2012 Jul;126(1):30-35.

ABBREVIATIONS

AI	Aromatase inhibitor
AR	Androgen receptor
BSO	Bilateral salpingo-oophorectomy
CA125	Cancer antigen 125
CI	Confidence interval
COX-2	Cyclooxygenase-2
CS	Carcinosarcoma
CT	Computerized tomography
ER-α/-β	Estrogen receptor-α/-β
ESS	Endometrial stromal sarcoma
Exp	Expected
FDG-PET	F-fluorodeoxyglucose positron emission tomography
FDG-PET-CT	F-fluorodeoxyglucose positron emission tomography with computerized tomography
FIGO	International Federation of Gynecology and Obstetrics
HNPCC	Hereditary nonpolypoid colon cancer
HPF	High-power field
HUCH	Helsinki University Central Hospital
IARC	International Agency for Research on Cancer
IHC	Immunohistochemistry, immunohistochemical
JEM	Job-exposure matrix
LMS	Leiomyosarcoma
LND	Lymph node dissection
MI	Mitotic index
MRI	Magnetic resonance imaging

NOCCA	Nordic Occupational Cancer Study
Obs	Observed
PR	Progesterone receptor
PRA/B	Progesterone receptor A/B
SEER	Surveillance, Epidemiology, and End Results program
SIR	Standardized incidence ratio
SPSS	Statistical Package for the Social Sciences
STUMP	Smooth muscle tumor of uncertain malignant potential
UES	Undifferentiated endometrial sarcoma
US	Uterine sarcoma
WT1	Wilms tumor gene 1

ABSTRACT

Uterine carcinosarcoma (CS), leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS), which have historically been considered as subtypes of uterine sarcomas (USs), represent only a small proportion of uterine malignancies. However, it has been estimated that USs account for nearly one third of deaths from uterine malignancies (Nordal and Thoresen 1997).

The aims of these studies were to assess clinical behavior, survival, prognostic markers and epidemiological aspects of uterine CS, LMS and ESS. In a retrospective study we analyzed survival and prognostic markers (both clinical and immunohistochemical) in patients treated from 1990 to 2001 at Helsinki University Central Hospital (HUCH). In the epidemiological studies the incidence and occupational risk of uterine LMS and ESS were examined by using the NORDCAN and Nordic Occupational Cancer Study (NOCCA) databases. A cohort of 8606 cases of USs from 13 cancer registries was used to evaluate the risk of a second primary malignancy after the first primary US. This study was coordinated by the International Agency for Research on Cancer (IARC).

The age-adjusted incidence of LMS was about 0.4–0.5 per 100 000 and that of ESS about 0.2 per 100 000 in Iceland, Denmark, Finland and Norway during the study period 1978–2007. Age-specific incidences were highest around menopause for both subtypes of USs. Shoe and leather workers, farmers and teachers showed elevated standardized incidence ratios (SIRs) as regards LMS. However, no occupations were associated with increased SIRs in connection with ESS.

One hundred patients with uterine CS (n = 40), LMS (n = 39) and ESS (n = 21) were treated in our institution during 1990–2001. The 2-, 5-, and 10-year disease-specific survival rates were 64%, 56% and 38% for all subtypes grouped together and 5-year survival rates for each subtype separately were 49% (CS), 57% (LMS) and 65% (ESS). Stage, age, tumor size and delivery status were independently associated with survival when all subtypes were combined. Immunohistochemical (IHC) analysis (n = 65) of ten markers showed that estrogen receptor-α (ER-α) and progesterone receptor (PR) positivity were associated with statistically significantly better disease-specific survival times and p53 positivity with worse disease-specific survival in patients with LMS.

The risk of a second primary cancer after the first primary US was analyzed in a cohort of 8606 cases of USs, in which 499 cancer cases were observed. Women with a primary US had a 26% increased risk (SIR 1.26, 95%CI 1.16–1.38) of developing a second primary cancer. SIRs were elevated as regards cancers of the mouth and pharynx (2.16, 95%CI 1.15–3.69), colorectum (1.60, 95%CI 1.28–1.98), lung (1.73, 95%CI 1.27–2.29), breast (1.25, 95%CI 1.05–1.49), urinary bladder (1.74, 95%CI 1.02–2.79), kidney (2.00, 95%CI 1.24–3.06), thyroid gland (2.74, 95%CI 1.42–4.79), and soft tissue sarcoma (5.23, 95%CI 2.51–9.62). The

risk of breast cancer increased along with increasing age at US diagnosis (p trend=0.040). The risk of kidney cancer increased along with lower age at the time of US diagnosis (p trend = 0.004) and short time since US diagnosis (p trend = 0.018).

In conclusion, the incidences of LMS and ESS showed constant trends in Nordic countries during the study period. Overpresentation of uterine LMS in shoe and leather workers and farmers might be associated with the etiology of LMS and this should be clarified in the future. Our institutional survival rates in cases of uterine CS, LMS and ESS were comparable with or even better than in earlier reports, and stage, age, tumor size, and delivery status of the patient emerged as the main prognosticators. Immunohistochemical expression of ER-α, PR and p53 were associated with survival of patients with LMS. After diagnosis of US there is an elevated risk of a second primary malignancy. Excesses of colorectal and urinary bladder cancers may reflect the effects of earlier treatments of US (radiotherapy and chemotherapy). The elevated risk of mouth and pharynx, lung and urinary bladder cancers after USs might be associated with common etiological factors such as smoking. The excesses of breast cancer in US patients may be related to a shared hormonal etiology.

INTRODUCTION

In 2010, 29197 incident cancers and 11677 cancer deaths were registered in Finland. According to the Finnish Cancer Registry, 14402 cancers and 1592 cancers of female reproductive organs were diagnosed in women during the same year (www.cancer.fi). More than 130000 incident cancers and nearly 60000 cancer deaths are observed in the Nordic countries every year (Engholm et al. 2010a). The number of new cancer cases has tripled in Finland during the last fifty years but the number of cancer deaths has stayed stable for many years (Pukkala et al. 2011).

Depending on the classification, 3% to 9% of malignancies of the uterine corpus and about 1% of all female genital tract malignancies are uterine sarcomas (USs, Nordal and Thoresen 1997, McMeekin 2007). The trend in incidence of malignancies of the uterine corpus has been increasing in Finland: 709 of these malignancies were registered per year from 1999 to 2003 and 804 in 2010. This category also includes USs in the Finnish Cancer Registry statistics (ICD-10 numbers C54.21, C54.22, C54.23 and C54.29). However, the exact number of USs is not shown in the statistics of the Finnish Cancer Registry (www.cancer.fi), but the estimated number of new USs is about 20 to 25 per year in Finland.

Knowledge of the etiology, risk factors and incidence of USs and second primary malignancies after USs is scanty, and no studies on occupational risks of USs exist. No consensus of treatment methods for USs in adjuvant or recurrent settings has been reached. In addition, survival figures as regards USs have been unchanged for several years, and no new prognosticators have emerged. In the present studies we focused on uterine carcinosarcoma (CS), leiomysarcoma (LMS) and endometrial stromal sarcoma (ESS), and our aim was to clarify epidemiological, clinical and prognostic aspects of these malignancies.

REVIEW OF THE LITERATURE

CLASSIFICATION OF UTERINE SARCOMAS

Uterine sarcomas are a heterogeneous group of malignancies. Historically, USs have been classified as carcinosarcomas (CSs, about 40% of cases), leiomyosarcomas (LMSs, 40%) and endometrial stromal sarcomas (ESSs, 15%) (McMeekin 2007). The remaining 5% consist of a heterogeneous group of vascular, lymphatic and heterologic sarcomas. Recent studies have revealed increasing evidence that CS is a subtype of endometrial carcinoma (McCluggage 2002a, McCluggage 2002c). The updated classification is as follows: LMS (60%), ESS (30%), undifferentiated endometrial sarcoma (UES, =undifferentiated uterine sarcoma, 5%) and adenosarcoma (5%) (Amant et al. 2009a). Nevertheless, CS is still included in many studies and reviews of US. The recent and historical classification of USs is summarized in Table 1.

Table 1. Classification of uterine sarcomas

Historical Classification of Uterine Sarcomas	**Recent Classification of Uterine Sarcomas**
Carcinosarcoma (40%)	-
Leiomyosarcoma (40%)	Leiomyosarcoma (60%)
Endometrial Stromal Sarcoma (15%) -low-grade -high-grade	 Low-grade Endometrial Stromal Sarcoma (30%) Undifferentiated Endometrial Sarcoma (5%)
Other uterine sarcomas (5%)	Adenosarcoma and other uterine sarcomas (5%)

EPIDEMIOLOGICAL ASPECTS

Incidence of uterine sarcomas

Uterine sarcomas represent up to 9% of uterine cancers (Nordal and Thoresen 1997, McMeekin 2007). In Finland, the age-adjusted incidence rate of US in 2003–2007 was 0.7 per 100 000 (NORDCAN database (Engholm et al. 2010a,b)). In Norway, the annual incidence rate of USs was as high as 1.7 per 100 000 females in 1987–1992 (Nordal and Thoresen 1997) and the incidence rate was the same in 1973–1981 in the United States (Harlow et al. 1986).

Risk factors of uterine sarcomas

Age and ethnic background

The sparse amount of data on the age-specific incidences of US has shown the peak incidences of LMS ranging from 45–49 (Harlow et al. 1986) to 50–64 years (Nordal and Thoresen 1997) and a peak incidence of ESS in the age group 50–64 years (Nordal and Thoresen 1997). The incidence of CS has been noticed to increase after menopause (Harlow et al. 1986, Nordal and Thoresen 1997).

Variation in US incidence has been reported among different races (Harlow et al. 1986, Platz and Benda 1995). The age-adjusted incidence among blacks has been twice that of whites and more than twice that of women of other races (Brooks et al. 2004).

Parity and obesity

Uterine sarcoma is a very rare malignancy in pregnant woman. However, the majority (38%) of 40 genital sarcomas reported during pregnancy over a period of 50 years of time, were USs according to a recently published review (Matsuo et al. 2009).

The incidence of US has been described as being higher among women never-married than women ever-married and it has been explained by nulliparity among never-married women (Schwartz and Weiss 1990). However, the association between parity and the risk of US is unclear: both lower risk (Kvale et al. 1988, Albrektsen et al. 1995) and no association have been described (Schwartz et al. 1991).

Obesity is a potential risk factor of US (Schwartz et al. 1996). Schwartz and co-workers reported elevated risks of CS, LMS and ESS among patients with a body mass index over 27kg/m2.

Smoking, hormonal treatment and radiation therapy

In only one study has smoking been investigated in connection with USs. Smoking was associated with lower risks of LMS (n = 56) and ESS (n = 26) but no association was found with CS (n = 85). The odds ratio was 0.6 (95% CI 0.3–1.1) for LMS and 0.5 (95%CI 0.1–1.2) for patients with ESS among women who had ever smoked cigarettes (Schwartz et al. 1996).

Long-term use of hormonal agents, both for contraception and replacement therapy, has been associated with a raised risk of US (Schwartz et al. 1996, Jaakkola et al. 2011). Women, who had used estradiol-progestin therapy for more than 5 years, had a 2.6-fold increased risk of LMS (Jaakkola et al. 2011). Tamoxifen treatment has also been linked to an elevated risk of US (Wickerham et al. 2002, Arenas et al. 2006).

An elevated risk of USs, especially CS, has been detected after pelvic radiation for malignant disease (Meredith et al. 1986).

Occupational risks of gynecological cancers

Cancer risks according to occupational affiliation reflect possible occupational carcinogenic exposure as well as lifestyle habits, cultural norms and the socioeconomic positions of certain occupational groups. The results of occupational cancer studies will help in the development of preventive actions and may give clues to etiological factors of different cancers. The limitations of these kinds of epidemiological studies can include the absence of data on confounding factors and lack of power to detect associations. It has been estimated that about 5% of all cancer cases in Finland may have been related to work in the time-period of 1971–1985 (Pukkala 1995).

Several studies of occupational risks and exposures in connection with gynecologic cancers have been published (Shen et al. 1998, Vasama-Neuvonen et al. 1999, Weiderpass et al. 2001, Shields et al. 2002, Pukkala et al. 2009, Riska et al. 2012). Weiderpass et al. found no occupational categories with a statistically significantly elevated relative risk of endometrial cancer, but for cervical cancer increased risks were detected among woodworkers, road and streetcar service personnel, painters, restaurant waitresses, textile inspectors, plywood and fiberboard workers and bar and cafeteria waitresses. When they linked cancer risks with job-exposure matrices (JEMs), endometrial cancer was associated with exposure to animal-related dust and sedentary work, and cervical cancer was associated with exposure to aliphatic,

alicyclic, aromatic and chlorinated hydrocarbon solvents, silica and wood dust (Weiderpass et al. 2001). In 2009 Pukkala et al. published the results of a study on a large Nordic cancer incidence cohort analyzed by occupational category. Artistic workers and dentists had the highest risks of endometrial cancer and female beverage worker and drivers presented the lowest risks in their report. On the other hand they noticed significantly increased cervical cancer rates among beverage workers, "other construction workers", waiters, tobacco manufacture workers, drivers and electrical workers and significantly decreased cervical cancer rates among dentists, physicians, teachers, farmers and nurses (Pukkala et al. 2009). Elevated ovarian cancer rates have been associated with occupations such as dry cleaning, telegraph and telephone work, paper packaging, graphic and printing work. Hairdressers and beauticians have also been reported to have an increased risk of ovarian cancer, but this finding is inconsistent. Organic dusts, aromatic amines, aliphatic and aromatic hydrocarbons have been suggested as specific etiologic agents for ovarian cancer in the JEM analyses (Shen et al. 1998, Vasama-Neuvonen et al. 1999, Shields et al. 2002). Riska et al. recently published a study of occupational risks in connection with primary fallopian tube carcinoma: significantly increased risks were observed among smelting workers, artistic workers, hairdressers, packers, nurses, shop workers and clerical workers. They also reported significantly low risks among women working in farming and among economically inactive women (Riska et al. 2012).

Second primary cancers after first primary gynecological cancer

In recent decades, cancer has become transformed from being a fatal disease to a disease that can be treated with very effective methods, and patients can either be cured or live for a longer time with cancer. This long-term survivorship has made the risk of second primary cancers more obvious. The raised incidence of second primary cancer after any malignancy could be a result of intensive surveillance after the first cancer diagnosis, the effects of different treatment modalities (chemo- and radiotherapy), and/or shared etiological, environmental and genetic factors between the first and second malignancy (Boice et al. 1985b). About 16% of new incident cancers reported in the SEER data were second- or higher order primary cancers in 2003 (Travis 2006).

The probability of developing an independent second primary malignancy after radiotherapy increases with time, and such malignancies are observed in the lining cells of the body and in tissues and organs that have received radiation (Hall and Wuu 2003). Typical second primary malignancies that can be induced by radiotherapy are solid tumors such as breast, thyroid, lung, stomach, colon, esophagus, bladder, ovary, brain and liver cancers (Travis 2006). Chemotherapy can be another risk factor as regards an increased incidence of second primary malignancies and the risk begins to increase from one to two years after treatment (Travis 2006, Grosse et al. 2009). A few chemotherapeutic agents have been linked to solid tumours:

cyclophosphamide to bladder cancer, mechlorethamine (+ nitrogen mustard), vincristine, procarbazine and prednisone combined chemotherapy to lung cancer and alkylating agents to bone sarcomas (Hawkins et al. 1996, Travis 2002, Grosse et al. 2009). Both chemo- and radiotherapy can cause leukemia, but occurrence after the use of cytotoxic drugs is more common.

Several studies concerning second malignancies after first primary female genital tract cancer have been published (Boice et al. 1985a, Curtis et al. 1985, Storm and Ewertz 1985, Bergfeldt et al. 1995, Kaldor et al. 1995, Travis et al. 1999, Weinberg et al. 1999, Hemminki et al. 2003, Ohno et al. 2006, Riska et al. 2007a, Srinivasan et al. 2007, Chaturvedi et al. 2009, Brown et al. 2010). Significantly increased risks have been reported as regards cancers of the breast, colon, esophagus, kidney, lung, oral cavity, ovaries, pharynx, rectum, urinary bladder, vagina, and vulva, and leukemias. Patients with ovarian cancer seem to have the greatest risk of developing a second primary malignancy (Curtis et al. 1985, Storm and Ewertz 1985, Bergfeldt et al. 1995). Genetic, environmental (infections, smoking, hormonal aspects), and treatment-related (chemo- and radiotherapy) factors and strict surveillance are thought to explain the increased risks after first primary gynecologic cancer.

In various studies significantly increased risks of a second primary malignancy at any site after endometrial cancer have been noticed (Curtis et al. 1985, Storm and Ewertz 1985, Bergfeldt et al. 1995, Hemminki et al. 2003, Brown et al. 2010). Curtis et al. (1985) reported a risk ratio (RR) of 1.30 (95%CI 1.22–1.38), Bergfeldt et al. (1995) and Hemminki et al. (2003) standardized incidence ratios (SIRs) of 1.21 (95%CI 1.12–1.30) to 1.54 (95%CI 1.48–1.61) for all second cancers. In the two other studies, SIRs were 0.99 (95%CI 0.99–1.14) and 1.04 (95%CI 0.96–1.01) (Storm and Ewertz 1985, Brown et al. 2010). In all studies significant excesses of colon cancers were noticed after first primary endometrial cancer. Other common sites with excesses of cancers have been the breast and urinary bladder. In a recent study, significantly decreased rates of second primary cancers have been detected at certain sites such as the oral cavity, pharynx and lung (Brown et al. 2010). The pattern of second neoplasms after endometrial cancer may be associated with genetic factors (HNPCC), treatment effects (colon, urinary bladder), shared etiological factors and intensive clinical surveillance.

In a study including more than 25,000 primary female genital tract cancers, second primary cancers were analyzed in a subgroup of 905 women with USs: a nonsignificantly increased risk (RR 1.30, 95%CI 0.96–1.72) as regards all sites combined was observed (Curtis et al. 1985).

CLINICAL FEATURES

Symptoms, signs and diagnosis

The clinical presentation of US is nonspecific. The most common symptom of US, regardless of the type, is abnormal vaginal pre- or postmenopausal bleeding (Giuntoli et al. 2003, Benoit et al. 2005, McMeekin 2007, Wu et al. 2011). The patient may have an enlarged uterus, a palpable abdominal mass, abdominal pain, or only a poor general condition, especially in cases with advanced-stage of the disease (Sagae et al. 2004, Benoit et al. 2005). Sometimes CS can cause a polypoid mass protruding from the cervix, which is noticed in a gynecological examination (McMeekin 2007, Wu et al. 2011). Patients with USs rarely have no symptoms at all (Benoit et al. 2005).

Preoperative diagnosis is demanding and problematic depending on the US subtype (Amant et al. 2009a). Correct preoperative diagnosis of malignancy has been reported in 93.5% of CSs, 35% of LMSs and 25% of ESSs and as regards preoperative sarcoma diagnosis in 24%, 23% and 20% of cases, respectively (Sagae et al. 2004). The reported incidence of US among patients operated upon for a benign leiomyoma or a rapidly growing leiomyoma has been only 0.23% (Parker et al. 1994).

Women with bleeding disorders and suspected malignancy are examined by way of endometrial biopsy or curettage. In cases of CS, endometrial biopsy samples frequently include only the epithelial component of the malignancy (McMeekin 2007). The difficulty of diagnosing LMS and ESS preoperatively by endometrial biopsies may be related to the mesechymal origin of the tumors. By means of endometrial cytology 52% of CSs, 15% of LMSs and 5% of ESSs have been reported to be correctly diagnosed (Sagae et al. 2004). Endometrial preoperative sampling (biopsy or curettage) has led to correct identification of malignancy in 86% (28/32 CS, 3/4 LMS and 2/2 ESS) and correct histologic diagnosis in 64% of the US cases. The detection rate in cases of invasive cancer was nearly equal among USs and endometrial carcinomas, but preoperative sampling was less reliable in predicting the correct histology of USs compared with epithelial tumors (Bansal et al. 2008). Cervical cytology (Pap smear) is of no benefit in the detection of US (Wang et al. 2002).

Imaging methods, such as ultrasonography, color Doppler ultrasonography, computerized tomography (CT) and magnetic resonance imaging (MRI), may help in diagnosing US. However, none of these can lead to precise preoperative diagnosis (Cacciatore et al. 1989, Sahdev et al. 2001, Amant et al. 2009a, Brocker et al. 2011, Wu et al. 2011). Even with MRI, the differentiation of LMS from a benign leiomyoma is demanding: a high signal intensity in T2-weighted images of large infiltrating myometrial masses is associated with LMS (Brocker et al. 2011, Wu et al. 2011). ESSs can be seen as invasive endometrial masses in MRI images (Sahdev et al. 2001) and they infiltrate either sharply or diffusely into the myometrium

(Koyama et al. 1999). MRI findings in CS are similar to those in endometrial adenocarcinoma and are indistinguishable in 88% of cases (Bharwani et al. 2010).

F-fluorodeoxyglucose positron emission tomography (FDG-PET) with computerized tomography (FDG-PET-CT), which combines both metabolic and anatomical findings in the evaluation of tumors (Rigo et al. 1996), might be useful in connection with metastatic or recurrent USs (Wu et al. 2011). In a small case series, use of FDG-PET allowed detection of all US cases, compared with detection rates 80% with MRI and 40% with power Doppler imaging (Umesaki et al. 2001). FDG-PET-CT has been reported to be highly sensitive and specific as regards detecting US recurrence during surveillance (Park et al. 2008a, Sharma et al. 2011), although no significant benefit over CT, MRI or ultrasonography was observed (Sharma et al. 2011).

Preoperative assay of the serum tumor marker CA125 is of limited value. In one study, 40% of cases of USs were reported to show elevated levels of CA125 before treatment (Duk et al. 1994). However, all sarcoma cells were negative in CA125 immunohistochemistry (IHC), and positivity was seen only in the epithelial component of CS (Duk et al. 1994). Raised CA125 levels have been associated with extrauterine disease and deep myometrial invasion in CS patients (Huang et al. 2007). Uterine leiomyomas can be associated with elevated levels of CA125 and this should be taken into account in the diagnostics of uterine LMS (He et al. 2011, Moore et al. 2012).

Histopathology

Carcinosarcoma is composed of both malignant epithelial and mesenchymal cells. The epithelial element is frequently endometrioid or serous and rarely clear cell, mucinous or squamous. The sarcomatous elements may be either homologous (tissues from the Műllerian tract such as endometrial stroma, fibrous tissue or smooth muscle) or heterologous (foreign tissues such as skeletal muscle, cartilage, bone or adipose tissue) (Tavassoli and Devilee 2003, D'Angelo and Prat 2011). Carcinosarcoma is still classified as a mixed epithelial and mesenchymal tumor (2003 WHO diagnostic criteria), although based on clinical and molecular evidence, CS is a poorly differentiated metaplastic carcinoma (McCluggage 2002c). The biphasic tumor components have an influence on the immunoprofile of CS and IHC expression of cytokeratins, epithelial membrane antigen, p53, desmin, myogenin, MyoD1, vimentin and even CD10 can be seen (D'Angelo and Prat 2010). By definition, CS is always a high-grade tumor.

Leiomyosarcoma is a malignant, hypercellular neoplasm composed of spindle cells from the smooth muscle compartment of the uterus. The tumor presents cellular atypia, tumor cell necrosis and a high mitotic index, which means over 15 mitotic figures per 10 high-power fields (HPFs). In addition to ordinary LMS, rare tumor variants such as epithelioid and

myxoid LMS exist (Tavassoli and Devilee 2003, D'Angelo and Prat 2010). The differential diagnosis of LMS from benign smooth muscle tumors and smooth muscle tumors of uncertain malignant potential (STUMP) has become easier since application of the 2003 WHO diagnostic criteria. For LMS, no grading system has been universally accepted (Tavassoli and Devilee 2003, Abeler et al. 2009).

In IHC of LMS, the expression of smooth muscle markers such as actin, desmin, h-caldesmon, and histone deacetylase is detected. Epithelioid LMS can express epithelial markers such as keratin and epithelial membrane antigen. The mesenchymal tumor marker vimentin is almost always positive in LMSs (McCluggage 2002b, D'Angelo and Prat 2010, Abeler and Nenodovic 2011). The expression of estrogen receptors (ERs), progesterone receptors (PRs) and androgen receptors (ARs) in LMS has varied from 0 to 100% (Bodner et al. 2003, Kitaoka et al. 2004, Leitao et al. 2004, Akhan et al. 2005, D'Angelo et al. 2009, Ioffe et al. 2009, Leitao et al. 2012). The ratio of ER-α /ER-β expression in LMSs was shown to be 0.06 in a recent study (Rodriguez et al. 2011), but usually only the expression of ER-α has been analyzed and reported. PR also exists as two isoforms, A and B. However, many commercial antibodies react with both isoforms, and investigators have not reported them separately. Expression of the proliferation marker Ki-67, p16 and p53 proteins, and various isoforms of the hyaluronate receptor CD44 can distinguish LMS from benign leiomyomas (Poncelet et al. 2001, Chen and Yang 2008). More than 50% of LMSs can react positively for CD10, a common acute lymphoblastic leukemia antigen (McCluggage et al. 2001, D'Angelo and Prat 2010, Abeler and Nenodovic 2011).

Endometrial stromal sarcoma is derived from the endometrial stromal cells, which are oval to spindle-shaped and infiltrate the myometrium. Small arterioles, foamy cytoplasmic cells, endometrial-type glands and even sex cord-like structures may be detected. Focal smooth muscle differentiation is less than 30%. The mitotic activity of ESS is usually low. ESS is a low-grade tumor by definition and high-grade endometrial stromal sarcoma is nowadays classified as undifferentiated endometrial sarcoma (UES) (Tavassoli and Devilee 2003). ESS is immunoreactive as regards CD10, vimentin, actin, keratin, ER and PR (Reich et al. 2000, Chu et al. 2001, D'Angelo and Prat 2010). Most ESSs have been reported to express ER-α, and both isoforms of PR. PRA has been the predominant isoform in one study (Balleine et al. 2004).

Adenosarcoma is a biphasic tumor, which consists of a benign epithelial component and a sarcomatous mesenchymal component. The epithelial component may show focal metaplastic changes. The mesenchymal part of adenosarcoma is usually a low-grade homologous stromal sarcoma with varying amounts of fibrous tissue and smooth muscle. Typically, mitotic figures are low in the mesenchymal component, and cytological atypia is mild. Adenosarcoma is immunoreactive as regards different cytokeratins, focally for CD10 and in varying degrees for smooth muscle markers (Tavassoli and Devilee 2003). Adenosarcomas lacking sarcomatous overgrowth also express ER and PR (Amant et al. 2004).

A undifferentiated endometrial sarcoma is a high-grade sarcoma without smooth muscle or endometrial stromal differentiation. This neoplasm shows marked cellular atypia, and high mitotic activity, and it resembles the sarcomatous component of CS. The aggressive growth pattern of UES typically displaces the myometrium. UESs are immunoreactive as regards Ki-67, p53 and p16 and usually no immunoreactivity is seen as regards ERs and PRs (Tavassoli and Devilee 2003, D'Angelo et al. 2009).

Altogether, a broad panel of ICH markers seems to be useful when analyzing uterine mesenchymal tumors (Zhu et al. 2004, Abeler and Nenodovic 2011).

Staging

USs are staged surgically and staging was defined by means of modified FIGO criteria for carcinomas of the endometrium until 2009 (Table 2, (International Federation of Gynecology and Obstetrics 2006)). In 2009 FIGO updated the staging system and introduced a new system for each type of US, except for CS, which is staged as carcinoma of the endometrium (Tables 3–5, (Mutch 2009)).

Table 2. FIGO staging system (1988) for carcinoma of the endometrium

Stage		Definition
Stage I		
	Ia	Tumor limited to endometrium, no myometrial invasion
	Ib	Less than half of myometrial invasion
	Ic	More than or equal to myometrial invasion
Stage II		
	IIa	Endocervical glandular involvement only
	IIb	Cervical stromal invasion
Stage III		
	IIIa	Tumor invades serosa and/or adnexa and/or positive peritoneal cytology
	IIIb	Vaginal metastases
	IIIc	Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV		
	IVa	Tumor invades bladder or bowel mucosa
	IVb	Distant metastasis

Table 3. FIGO staging system (2009) for LMS and ESS

Stage		Definition
Stage I		Tumor limited to uterus
	IA	Less than or equal to 5cm
	IB	More than 5 cm
Stage II	II	Tumor extends beyond the uterus, within the pelvis
	IIA	Adnexal involvement
	IIB	Involvement of other pelvic tissue
Stage III		Tumor invades abdominal tissues (not just protruding into the abdomen)
	IIIA	One site
	IIIB	More than one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV		
	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis

Table 4. FIGO staging system (2009) for adenosarcoma

Stage		Definition
Stage I		Tumor limited to uterus
	IA	Tumor limited to endometrium/endocervix with no myometrial invasion
	IB	Less than or equal to half myometrial invasion
	IC	More than half myometrial invasion
Stage II		Tumor extends beyond the uterus, within the pelvis
	IIA	Adnexal involvement
	IIB	Involvement of other pelvic tissue
Stage III		Tumor invades abdominal tissues (not just protruding into the abdomen)
	IIIA	One site
	IIIB	More than one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV		
	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis

Table 5. FIGO staging system (2009) for carcinoma of the endometrium

Stage		Definition
Stage I		Tumor limited to uterus, no involvement of uterine serosa
	IA	Less than or equal to half myometrial invasion
	IB	More than half of myometrial invasion
Stage II		Tumor invades cervical stroma but does not extend beyond the uterus
Stage III		Tumor involves the uterine serosa, adnexae, vagina, or retroperitoneal lymph nodes
	IIIA	Involvement of uterine serosa, and/or the adnexae
	IIIB	Vaginal involvement
	IIIC	Involvement of retroperitoneal lymph nodes
	IIIC1	Positive pelvic nodes
	IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV		Tumor involves rectal or bladder mucosa and/or distant organs
	IVA	Tumor invades mucosa of the rectum or bladder
	IVB	Distant metastasis

Treatment

Surgery

The treatment of USs has been based on surgery for years. The surgical gold standard has been extrafascial hysterectomy, with or without bilateral salpingo-oophorectomy (BSO) and pelvic lymph node dissection (LND). The diversity of histologic subtypes and different clinical behavior has influenced surgical recommendations.

The surgical treatment of CS comprises hysterectomy with BSO, systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy and comprehensive peritoneal staging (peritoneal cytology, omentectomy and peritoneal biopsies) (Gadducci et al. 2008, McMeekin 2007). Extended surgery is indicated by a reported high rate of lymph node (14-38%) (Callister et al. 2004, Nemani et al. 2008, Galaal et al. 2009) and adnexal metastases (22%) (Callister et al. 2004). Lymphadenectomy has been associated with improved survival, and in early-stage disease, the lymph node count has also correlated with the risk of recurrence and with survival (Temkin et al. 2007, Nemani et al. 2008). The survival of advanced-stage patients with CS (stages IIIC–IVB) has been shown to be better when no macroscopic residual tumor is left after cytoreductive operation (Tanner et al. 2011).

For LMS, which is mainly spread via the bloodstream rather than the lymphatic system, and ESS, the value of LND is low and the surgical treatment recommendation is simple hysterectomy (Gadducci et al. 2008, McMeekin 2007, Amant et al. 2009a, Nam 2011). Lymph node metastases are observed in about 11% of LMS cases (Giuntoli et al. 2003, Leitao et al. 2003, Kapp et al. 2008), but in earlier series the rates have been much higher, from 26% to 75% (Chen 1989, Goff et al. 1993, Gadducci et al. 1996). In cases of ESS, the most common incidence of lymph node metastasis has been less than 10% (Goff et al. 1993, Chan et al. 2008, Shah et al. 2008), although higher rates of up to 33% have also been reported (Riopel et al. 2005). Both with LMS and ESS patients, LND should be carried out as a cytoreductive procedure if the disease is extrauterine or if bulky lymph nodes are found during primary surgery (Gadducci et al. 2008, Amant et al. 2009a, Nam 2011).

A debate concerning oophorectomy among LMS patients has been ongoing for a long time. The reported incidence of ovarian metastasis has been only 4% (Leitao et al. 2003). Nowadays BSO is recommended for postmenopausal women with LMS. For premenopausal women, preservation of macroscopically normal ovaries is possible (Gadducci et al. 2008, Amant et al. 2009a, Nam 2011), since the risk of recurrence has not been found to increase with ovarian preservation (Gadducci et al. 1996, Giuntoli et al. 2003). In one study, the survival of young LMS patients (matched by age, grade and stage) was the same among cases with and without oophorectomy (Giuntoli et al. 2003).

Oophorectomy is recommended for ESS patients, because most ESSs are hormone-sensitive diseases (McMeekin 2007). Beck et al. reported that the recurrence rate was lower among

ESS patients who underwent BSO in primary operation (Beck et al. 2012). However, in recent studies the survival of premenopausal women with early-stage ESS with and without oophorectomy has been shown to be the same (Amant et al. 2007, Shah et al. 2008, Chan et al. 2008), and therefore individualization of the surgical approach is recommended in this group of patients (Amant et al. 2009a, Nam and Park 2010). In addition, the incidence of adnexal metastasis has been 13% and it usually occurs with macroscopically abnormal adnexes and extrauterine disease (Dos Santos et al. 2011).

Management of menopausal symptoms with estrogens is not recommended for ESS patients because of the high rate hormone-sensitivity of this tumor type (Chu et al. 2003, Pink et al. 2006, Amant et al. 2009a). The same recommendation and individual caution could be applied among patients who have hormone receptor-positive LMS, although the literature on this matter is scanty (Burger et al 1999, Ursic-Vrscaj 1999).

The surgical procedures are summarized in Table 6.

Table 6. Surgical procedures in cases of uterine carcinosarcoma (CS), leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS)

	Hysterectomy	BSO	LND	Omentectomy	Peritoneal cytology/biopsies
CS	+	+	+*	+	+/+
LMS	+	±	-	-	+/-
ESS	+	+	-	-	+/-

BSO = bilateral salpingo-oophorectomy, LND = lymph node dissection, *pelvic and para-aortic

Adjuvant therapies

Only a few prospective controlled trials of adjuvant therapies for USs have been carried out. When grouping all subtypes, neither radiotherapy nor chemotherapy has improved survival in adjuvant settings (Sagae et al. 2004, Benoit et al. 2005, Hensley 2011, Sampath and Gaffney 2011). However, radiotherapy may reduce the risk of local recurrence (Chauveinc et al. 1999, Gadducci et al. 2007, Sampath and Gaffney 2011).

Chemotherapy

Chemotherapy is a standard treatment both for completely resected and metastatic CS (Gadducci et al. 2008, Hensley 2011) because there is an extremely high risk of recurrence. About 50% of early-stage diseases and about 90% of advanced-stage diseases will recur (McMeekin 2007). For CS, active cytotoxic drugs are carboplatin, cisplatin, ifosfamide and paclitaxel (Gadducci et al. 2008, Homesley et al. 2007, Wolfson et al. 2007, Makker et al.

2008, Powell et al. 2010, Hensley 2011). Combinations of ifosfamide and carboplatin, or carboplatin and paclitaxel have been demonstrated to be the most beneficial regimens in first-line therapy, both in early- and advanced-stage CS (Hensley 2011). In stage III/IV, persistent, or recurrent CS the response rates in connection of these combination therapies have ranged from 45 to 62% (Homesley et al. 2007, Powell et al. 2010, Lacour et al. 2011).

The suggested standard procedure in cases of totally resected, uterus-limited LMS is observation (Amant et al. 2009a, Hensley 2011). However, the estimated risk of recurrence is more than 50% in patients with LMS, even in early-stage disease (Dinh et al. 2004), and therefore adjuvant chemotherapy is also used among patients who have completely resected, high-grade LMS. Traditionally, chemotherapy has been recommended in advanced-stage, inoperable or recurrent LMS, in which case the treatment is usually non-curative (Kanjeekal et al. 2005, Amant et al. 2009a). For years, patients with LMS have been subjected to various doxorubicin-based regimens in first-line treatment because of the documented efficacy of doxorubicin in connection with LMS (Omura et al. 1983, Omura et al. 1985, Sutton et al. 1996a, Pautier et al. 2004). Response rates have been 20–30% in cases of advanced or recurrent LMS (Omura et al. 1983, Muss et al. 1985, Omura et al. 1985, Sutton et al. 1996a). Better response rates (27% to 53%) were achieved in three prospective phase II trials with fixed-dose rate gemcitabine and docetaxel in the treatment of unresectable or metastatic LMS, after which this regimen was accepted as a first-line regimen in metastatic and relapsed disease (Hensley et al. 2002, Hensley et al. 2008a, Hensley et al. 2008b). In 2009, Hensley et al. published the results of a prospective study of women with completely resected stage I–IV LMS treated with four cycles of fixed-dose rate gemcitabine plus docetaxel: 45% of all treated patients remained disease-free at 2 years (Hensley et al. 2009a). In the SARC005 study, women with completely resected stage I–III, high-grade LMS received four cycles of fixed-dose rate gemcitabine plus docetaxel, followed by four cycles of doxorubicin: 78% of the patients remained progression-free at 2 years (Hensley et al. 2010).

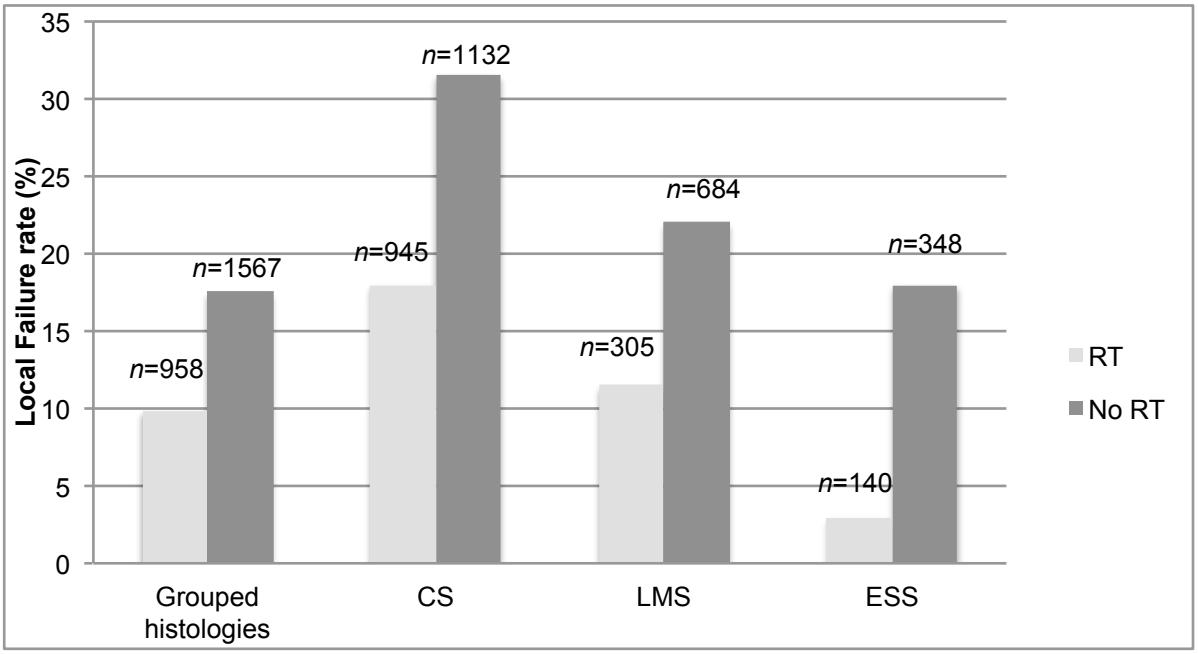
Trabectedin has proven activity among patients with locally advanced or metastatic LMS, and this new regimen may be a therapeutic option after first- or second-line treatment failures with gemcitabine and docetaxel, and doxorubicin-based regimens (Amant et al. 2009b, Ray-Coquard 2011, Sanfilippo et al. 2011). In a recent phase II study, the activity of trabectedin was assessed in the first-line treatment of advanced, persistent and recurrent uterine LMS: only 10% of the patients had a partial response, 50% had stabilized disease, and the median progression-free survival period was 5.8 months (Monk et al. 2012).

For completely resected ESS, no adjuvant chemotherapy is normally recommended (Gadducci et al. 2007, Amant et al. 2009a, Hensley 2011). Advanced stage or hormone-unresponsive diseases should be treated with active cytotoxic agents, such as ifosfamide and doxorubicin (Sutton et al. 1996b).

Radiotherapy

Recommendations concerning adjuvant radiotherapy in the treatment of USs vary and are mainly based on the results of retrospective studies (Sampath and Gaffney 2011). Only two randomized-controlled phase III studies have been published (Wolfson et al. 2007, Reed et al. 2008). For early-stage CS, improved local control is the strongest evidence for adjuvant pelvic radiotherapy (Sampath and Gaffney 2011). Adjuvant radiotherapy for LMS and ESS patients is thought to be non-beneficial (Reed et al. 2008, Amant et al. 2009a, Barney et al. 2009), but with both subtypes there is tendency to show improved local control compared with patients treated by means of surgery alone (Figure 1: modified from that by Sampath and Gaffney (2011)).

Figure 1. Local failure rate (%) as regards different types of uterine sarcomas after using adjuvant radiotherapy (RT) or no adjuvant radiotherapy



n = number of uterine sarcoma cases in different studies, CS = carcinosarcoma, LMS = leiomyosarcoma, ESS = endometrial stromal sarcoma

Endocrine therapy

Older data showed that hormone therapy (medroxyprogesterone acetate, tamoxifen, or both) was ineffective among US patients (Wade et al. 1990). For a long time, ESS was thought to be the only subtype of US that responds to hormonal manipulation (Garrett and Quinn 2008). However, both ESS and LMS express ERs, PRs and ARs to different degrees, but hormone receptor expression of CS is almost always negative (D'Angelo et al. 2009, D'Angelo and Prat 2010).

The suggested mechanisms of different hormone therapies are as follows: progestins exert an anti-estrogenic effect through binding to the PRs, aromatase inhibitors (AIs) block the

conversion of androgens to estrogens in peripheral-fat tissue and the antiprogestin mifepristone, which is a selective PR modulator, acts via competitive interaction with progesterone at PR sites, or it can produce a progesterone-like effect in the absence of progesterone (Ramondetta et al. 2009, Bouchard et al. 2011). The anti-cancer activity of mifepristone is also likely to be multifactorial and mifepristone has been shown to inhibit the growth of different cancer cell lines even without the necessity of nuclear PR (Tieszen et al. 2011). The anti-estrogen tamoxifen is nowadays associated with an increased risk of US, which might be caused by its estrogenic activity in endometrial stroma and glands (Wickerham et al. 2002, Chu et al. 2003, Arenas et al. 2006).

For patients with CS, hormone therapy is usually useless, because these tumors are mostly hormone receptor-negative. However, in a few cases of recurrent or advanced CS progestin therapy has brought about stabilization of the disease, lasting from 3 to 34 months (Ioffe et al. 2009).

Many case reports and studies on series have been published as regards hormone therapy for LMS and ESS, especially with progestins (medroxyprogesterone and megestrol) and AIs (letrozole and anastrazole), both in adjuvant settings and in cases of recurrent or advanced disease (Uchida et al. 1996, Maluf et al. 2001, Leunen et al. 2004, Pink et al. 2006, Hardman et al. 2007, Ioffe et al. 2009, O'Cearbhaill et al. 2010). For ESS patients, 76% of cases have reported to respond to progestins and nearly 88% to AIs (Amant et al. 2009a). Low-grade ESS has also reported to express aromatase in IHC analysis (Reich and Regauer 2004). Patients with recurrent LMS have shown partial clinical responses to progestin or AI therapy in case reports (Uchida et al. 1996, Hardman et al. 2007). In two retrospective studies, 40% to 100% of patients with recurrent or advanced LMS treated with AIs responded to therapy (stable disease or partial response) (Ioffe et al. 2009, O'Cearbhaill et al. 2010). In a recent review it was concluded that AIs seem to have an effective role in the treatment of ESS and might help to stabilize LMS progression (Altman et al. 2012). Phase II studies of letrozole in the treatment of LMS (adjuvant and recurrent settings) are ongoing in the United States (http://clinicaltrials.gov).

Two case reports of patients with recurrent ESS treated with a gonadotropin-releasing hormone analog alone or with progestin have been published (Burke and Hickey 2004, Dupont and Disaia 2010). In these reports, a partial response and a complete response were achieved, respectively. In a small phase II trial, twelve patients with advanced or recurrent endometrioid adenocarcinoma (n = 10) or low-grade ESS (n = 2) were treated with mifepristone. The treatment resulted in stable disease in 25% of all patients and one of the two ESS patients (Ramondetta et al. 2009).

Nowadays hormone therapy is accepted as one type of targeted treatment, with benefit in hormone receptor-positive uterine LMS and ESS (Amant et al. 2009a, Sjoquist et al. 2011, Altman et al. 2012). Good patient compliance is achieved with these therapies because all hormone therapies have been well tolerated with no appreciable side effects (Ioffe et al. 2009, Ramondetta et al. 2009, O'Cearbhaill et al. 2010, Altman et a. 2012).

Targeted treatment

Several biomolecular treatment options have been studied, mainly in phase II trials, in cases of USs or soft-tissue sarcomas (Amant et al. 2009a, Hensley 2011). Different tyrosine kinase inhibitors, such as imatinib, sunitinib, sorafenib and pazopanib have been assessed in cases of recurrent or persistent USs and STSs: response rates have been less than 10% (Hensley et al. 2009b, Maki et al. 2009, Sleijfer et al. 2009, Huh et al. 2010). Bevacizumab, which is a monoclonal antibody that inhibits vascular endothelial growth factor A, has been added to doxorubicin (D'Adamo et al. 2005) or gemcitabine and docetaxel treatment in phase I/II trials in cases of advanced soft tissue sarcomas (Verschraengen et al. 2008). D´Adamo et al. reported partial responses in two patients (2/7, 28%) with uterine LMS and Verschraengen et al. in two patients who had no site-specified LMS (2/5, 40%). In both studies the combinations showed activity in advanced soft tissue sarcomas even thought the cardiac toxicity of doxorubicin and adverse events associated with bevacizumab warrant further studies. A phase III study of gemcitabine and docetaxel with or without bevacizumab in the treatment of patients with advanced or recurrent uterine LMS is ongoing in the United States (http://clinicaltrials.gov).

In future, possible targets for therapy of US could be Wilms tumor gene 1 (WT1) and cyclooxygenase-2 (COX-2, tumor growth and metastasis promoting enzyme) (Amant et al. 2009a). COX-2 has been found to be overexpressed in uterine LMS and WT1 in uterine CS, LMS, ESS and UES (Coosemans et al. 2007, Tesfaye et al. 2007). WT1 might be an attractive target for immunotherapy of USs, and COX-2 inhibitors (sulindac, celecoxib) could be used in COX-2-positive LMSs (Amant et al. 2009a).

Recurrent disease

More than 50% of patients with primary CS and LMS who have completely responded will relapse (Dinh et al. 2004, McMeekin 2007, Abeler et al. 2009). Even though ESS is a low-grade disease, recurrences may develop in as many as a third to a half of patients over a long period of time (Chang et al. 1990). Typical sites for recurrences of USs are the pelvis, liver and lungs (McMeekin 2007).

Surgery, radiotherapy, chemotherapy, hormone therapy or a combination of these treatments is an option for relapsed US. For LMS and ESS, all treatment modalities are possible, and surgery (sometimes repeatedly) is the best choice if a single metastasis, for example in the liver or lungs, is diagnosed (Amant et al. 2009a). Recurrence of CS is mainly treated by means of chemotherapy, as is the case in most multiple site recurrences of LMS and ESS. The same cytotoxic drugs as in adjuvant treatment are utilized, and 0–57% of all cases of recurrent US have been reported to respond to various forms of chemotherapy (Kanjeekal et al. 2005).

Before starting hormone therapy, receptor status should be determined (Amant et al. 2009a). Radiotherapy is a possible choice for palliative, symptom-relieving treatment in all cases of recurrent US.

The treatment options for uterine CS, LMS and ESS are summarized in Figures 2–4. The Figures are modified from Amant, IGCS 2010, Prague, and Amant et al. (2009a).

Figure 2. Clinical management of uterine carcinosarcoma

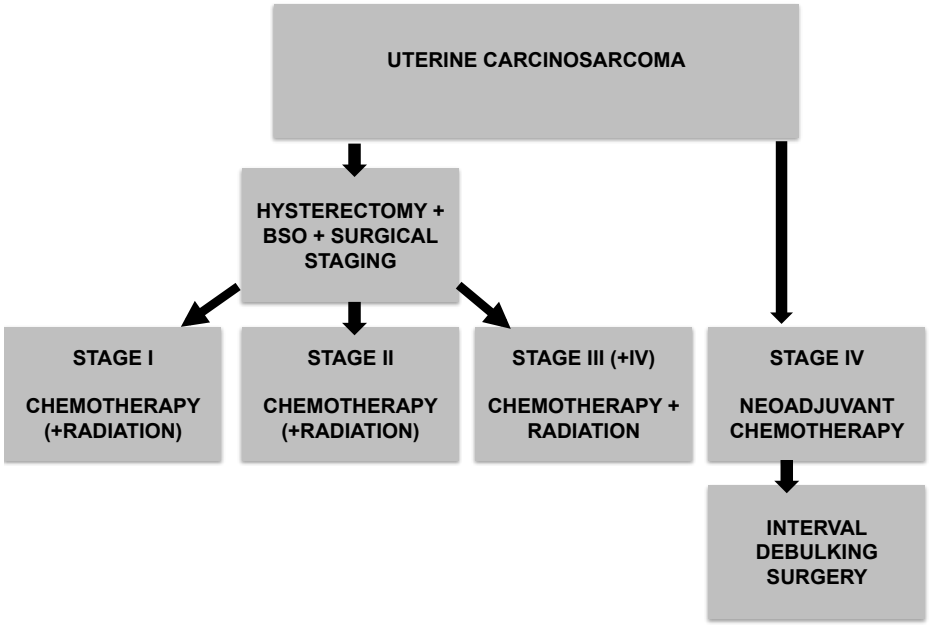
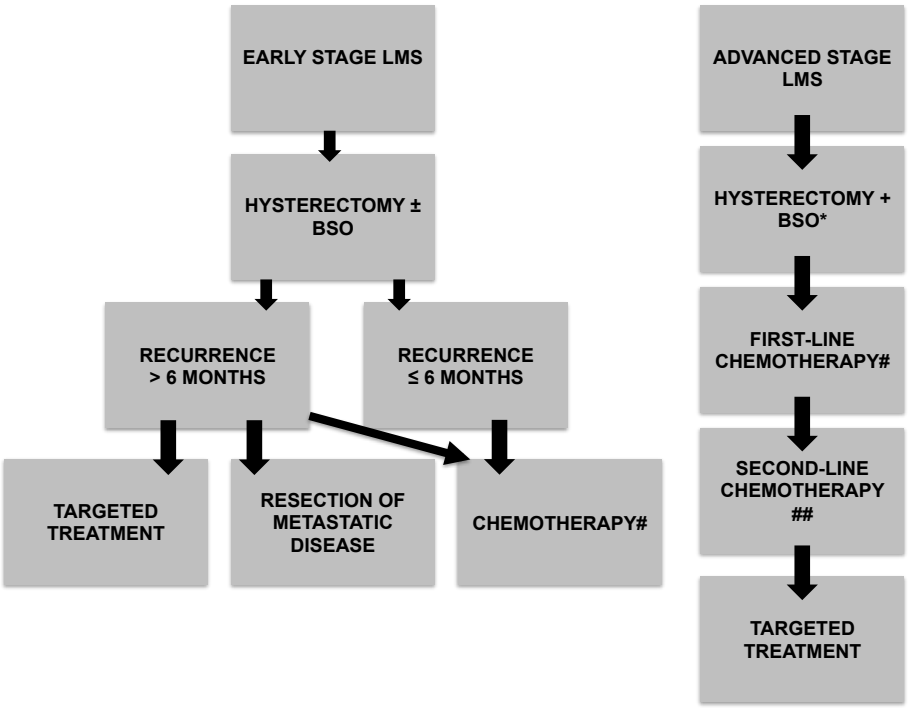
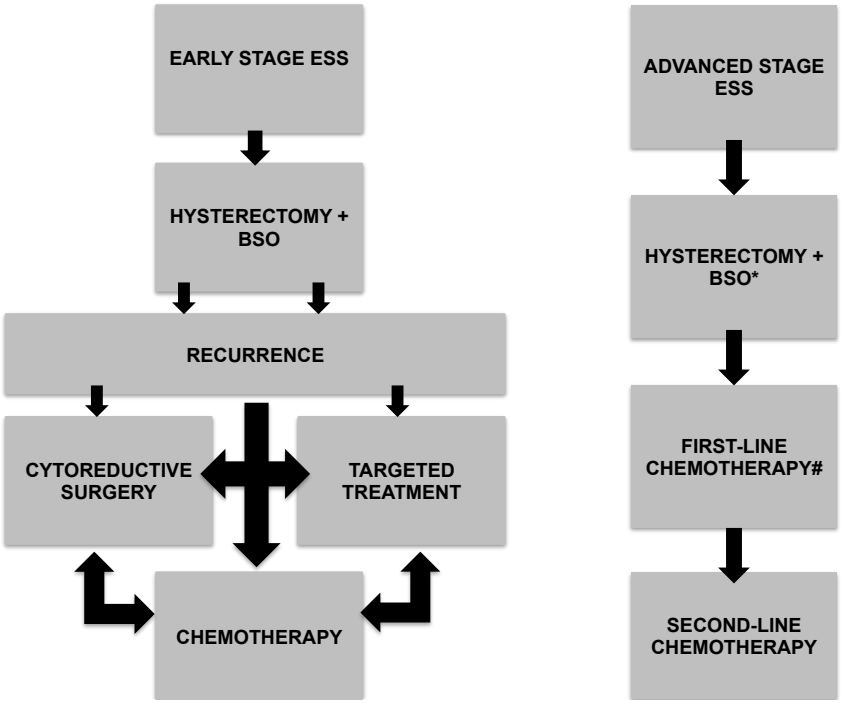


Figure 3. Clinical management of uterine leiomyosarcoma (LMS)



*if possible, #gemcitabine-docetaxel, ##doxorubicin/ifosfamide-doxorubicin,
BSO = bilateral salpingo-oophorectomy

Figure 4. Clinical management of endometrial stromal sarcoma (ESS)



*if possible, #ifosfamide-doxorubicin, BSO = bilateral salpingo-oophorectomy

Survival

The best 5-year survival rates are found among patients with ESS and the worst among patients with CS and LMS. Overall 5-year survival in all cases of uterine sarcoma has varied from 17% to 59% in different reports (Table 7). Five-year survival rates in cases of CS, LMS and ESS are summarized in Tables 8–10.

Table 7. Type distribution and 5-year survival (%) in cases of uterine sarcoma

Study	*n*	CS *n* (%)	LMS *n* (%)	ESS *n* (%)	Other sarco-mas *n* (%)	Study period	5-year overall survival
Nieminen et al. 1974	117	9 (8)	71 (61)	17 (14)	20 (17)	1937–1964	54.7
Kahanpää et al. 1986	119	45 (38)	51 (43)	23 (19)	0 (0)	1958–1977	42
Olah et al. 1992	423	152 (36)	215 (51)	26 (6)	30 (7)	1967–1981	31
Nordal and Thoresen 1997	1042	284 (27)	476 (46)	124 (12)	158 (15)	1971–1975 1983–1987	50.2# 48#
Chauveinc et al. 1999	73	23 (32)	32 (44)	14 (19)	4 (5)	1975–1995	45
Pautier et al. 2000	157	52 (33)	78 (59)	27 (17)	0 (0)	1976–1995	40
el Husseiny et al. 2002	59	20 (34)	25 (42)	14 (24)	0 (0)	1980–1997	48*
Gadducci et al. 2002	249	101(41)	95 (38)	53(21)	0 (0)	1980–1994	41.6
Brooks et al. 2004	2677	NR	NR	NR	NR	1989–1999	42–53#
Livi et al. 2005	40	12 (30)	24 (60)	3 (8)	1 (2)	1980–2001	25**
Benoit et al. 2005	72	25 (35)	34 (47)	12 (17)	1 (1)	1966–2001	36.1
Kokawa et al. 2006	97	46 (47)	36 (37)	15 (16)	0 (0)	1990–2003	17.5
Denschlag et al. 2007	94	36 (56)	30 (32)	28 (30)	0 (0)	1989–2004	47
Park et al. 2008	127	44 (35)	46 (36)	37 (29)	0 (0)	1987–2007	59
Abeler et al.2009	419	-	259 (62)	85(20)	75(18)	1970–2000	NR
Albrektsen et al. 2009b	493	118 (24)	249 (51)	126 (26)	0 (0)	1960–1999	NR

CS = carcinosarcoma, LMS = leiomyosarcoma, ESS = endometrial stromal sarcoma, NR = not reported, # relative, *Estimate from the figure published by el Husseiny et al., **5-year disease-specific survival %

Table 8. Five-year survival (%) by stage in cases of uterine carcinosarcoma

Study	*n*	Stage I	Stage II	Stage III	Stage IV	All stages
Nordal et al. 1997	46	40	25	15	0	31
Blom et al. 1998b	44	53.5 (stage I-II)*	-	20 (stage III-IV)*	-	38
Sagae et al 2004	46	78.8	80	41.6	0	NR
Callister et al 2004	300	37	21	27	-	31
Galaal et al. 2009	93	46 (stage I-II)	-	10 (stage III-IV)*	-	33
Gonzalez Bosquet et al. 2010	121	59 (stage I-II)	-	22	9	NR
Nieminen et al. 1974	9					33.3
Kahanpää et al. 1986	45					33
Nordal and Thoresen 1997	284					36.8–44
Chauveinc et al. 1999	23					35
Pautier et al. 2000	52					37
Benoit et al. 2005	25					34.8
Kokawa et al. 2006	46					16.7
Denschlag et al. 2007	36					23
Nemani et al. 2008	1855					49#–34##
Albrektsen et al. 2009b	118					55

NR = not reported, #/##Lymph node dissection done/not done, *Estimate from the figure published by Blom et al., Galaal et al.

Table 9. Five-year survival (%) by stage in cases of uterine leiomyosarcoma

Study	*n*	Stage I	Stage II	Stage III	Stage IV	All stages
Giuntoli et al.2003	208	62*	45*	35*	20*	NR
Sagae et al. 2004	40	73	100	0	0	NR
Wu et al. 2006	51	73*	-	43* (Stage III-IV)	-	67.4
Kapp et al. 2008	1396	75.8	60.1	44.9	28.7	65.7
Nieminen et al. 1974	71					66.2
Kahanpää et al. 1986	51					39
Gadducci et al. 1996	126					40**
Nordal and Thoresen 1997	476					45.9–50.4
Chauveinc et al. 1999	32					33
Mayerhofer et al. 1999	71					65
Pautier et al. 2000	78					35
Benoit et al. 2005	34					30.2
Kokawa et al. 2006	36					16
Denschlag et al. 2007	30					40
Abeler et al. 2009	235					43#
Albrektsen et al. 2009b	249					68

NR = not reported, *Estimate from the figure published by Giuntoli et al., Wu et al., **5-year disease-free survival %, estimate from the figure published by Gadducci et al., #Estimate from the figure published by Abeler et al.

Table 10. Five-year survival in cases of endometrial stromal sarcoma

Study	*n*	All stages
Nieminen et al. 1974	17	52.9
Kahanpää et al. 1986	23	61
Nordal et al. 1996	48	69
Nordal and Thoresen 1997	124	73–83.7
Chauveinc et al. 1999	14	84
Pautier et al. 2000	27	57
Bodner et al. 2001	31	62
Sagae et al. 2004	20	94.7*
Benoit et al. 2005	12	58.5
Kokawa et al. 2006	15	25
Denschlag et al. 2007	28	82
Chan et al 2008	831	76.2
Abeler et al. 2009	85	76**
Albrektsen et al. 2009b	126	74

*Stage I, **Estimate from the figure published by Abeler et al.

PROGNOSTIC FACTORS

Age

Advancing age of patients with CS, LMS and ESS has been related to an unfavorable clinical outcome, both in univariate and multivariate analysis in almost all studies (Chan et al. 2008, Kapp et al. 2008, Nemani et al. 2008, Gadducci 2011). It has been reported that women with LMS aged over 50 had an 11.07-fold and women with ESS aged over 55 had a 6.47-fold increased risk of death (Wu et al. 2006, Garg et al. 2010).

Ethnic background

In recent SEER studies, black race has been an independent, negative predictor of survival among patients with CS, LMS and ESS (Chan et al. 2008, Kapp et al. 2008, Nemani et al. 2008). In earlier SEER data, white women with stage I US of all subtypes showed better 5-year relative survival than African-American women, but this difference was diminished when adjusting for adjuvant treatment of US (Brooks et al. 2004). Brooks and co-authors concluded that the poorer survival could be associated with a lower rate of referral to health care or less frequent use of adjuvant therapies (Brooks et al. 2004).

Parity

Studies in which parity has been evaluated as a prognostic factor of US are sparse. Nulliparity has been found to adversely affect the survival of patients with CS in one study (Marth et al. 1997). Sagae et al. reported an opposite finding among patients with CS (Sagae et al. 2004). In two other studies, parity has had no effect on the survival of patients with CS (Nordal et al. 1997, Bodner-Adler et al. 2001). In a recent study of 126 patients with ESS, 249 patients with LMS and 118 patients with CS, nulliparity was associated independently with poorer survival only among ESS patients ($p = 0.058$) (Albrektsen et al. 2009b).

Grade

Carcinosarcoma is by definition a high-grade tumor and ESS a low-grade tumor, and with these subtypes grade should not be assessed as a prognostic variable (Tavassoli and Devilee

2003). Historically, patients with high-grade ESS, nowadays classified as UES, have had poorer outcome than those with low-grade ESS (Nordal et al. 1996). In most studies, high-grade LMS has been associated with worse prognosis (Olah et al. 1992, Giuntoli et al. 2003, Kapp et al. 2008), but studies showing no association have also been published (Nordal et al. 1995, Wu et al. 2006).

Histology

The prognostic value of the histological subtype of US has been established in only a few studies (Nordal and Thoresen 1997, Gadducci et al. 2002). In a Norwegian study, the survival of patients with ESS was better than that of patients with LMS and CS ($p < 0.001$) (Nordal and Thoresen 1997). In an Italian study, the risk of death was significantly lower among patients with low-grade ESS (RR 0.257 95%CI 0.071–0.931) and CS (RR 0.509, 95%CI 0.324–0.799) compared with patients with LMS (Gadducci et al. 2002).

Immunohistochemistry

Several immunohistochemical markers have been studied as prognostic factors of USs (Gadducci 2011). Many investigators have looked at the prognostic clinical significance of the hormone receptors ER, PR and AR (Leitao et al. 2004, Akhan et al. 2005, Huang et al. 2007, Huang et al. 2009, Ioffe et al. 2009, Leitao et al. 2012). ER-α expression has been associated with a reduced risk of death and ER-β expression with a negative predictive value among CS patients (Huang et al. 2007, Huang et al. 2009). ER- and PR-positivity have been associated with better survival among LMS patients (Leitao et al. 2004, Akhan et al. 2005, Leitao et al. 2012), and ER expression has been associated with improved overall survival in all cases of US (Ioffe et al. 2009).

Overexpression of the mutant protein p53 has been demonstrated to be a prognostic factor as regards uterine LMS (Blom et al. 1998a, Anderson et al. 2006, Kim et al. 2006, D'Angelo et al. 2009). However, Nordal et al. found no impact of p53 accumulation on prognosis of US (all subtypes combined) and similar results have been published among patients with CS and ESS (Blom et al. 1998b, Iwasa et al. 1998, Nordal et al. 1998, Blom et al. 1999). Low Ki-67 expression has been linked to better survival of LMS patients and longer recurrence-free survival of ESS patients (Popiolek et al. 2003, Mayerhofer et al. 2004, Akhan et al. 2005, D'Angelo et al. 2009). Overexpression of the mutant protein p16 has been associated with a negative effect on the survival of LMS patients, and the oncogene *Twist*, which inhibits apoptosis, might be associated with worse survival of LMS patients ($p = 0.07$) (D'Angelo et al. 2009).

In recent studies COX-2, WT1 and Bcl-2 (apoptosis marker) have been evaluated in cases of US. COX-2 was observed to be an independent negative prognostic marker as regards LMS (Lee et al. 2011) and WT1 as regards LMS, CS and UES (Coosemans et al. 2011). Positive immunostaining of Bcl-2 protein in LMSs was associated with a longer time to recurrence and a longer period of overall disease-specific survival (Leiser et al. 2006, D'Angelo et al. 2009) and this marker could be used in combination with tumor size, mitotic index and Ki-67 expression (D'Angelo et al. 2011).

Lymphovascular space involvement

In a few studies the significance of lymphovasclular space involvement (LVI) in cases of US has been evaluated. It has been shown to be a marker of recurrence and relatively poor survival among CS and LMS patients (Major et al. 1993, Mayerhofer et al. 1999, Yamada et al. 2000).

Mitotic index

The mitotic index (MI) represents the number of mitotic figures per 10 HPFs in the most active area. The prognostic relevance of the MI in the sarcomatous component of CSs has not been established, but it has been reported to be a significant prognostic marker in cases of LMS and ESS. However, MI cut-off values have varied in different studies (Wolfson et al. 1994, Gadducci et al. 1996, Nordal et al. 1996, Abeler et al. 2009, Ayhan et al. 2009, D'Angelo et al. 2011, Gadducci 2011).

Stage

Stage is the strongest and most important prognostic variable in connection with all subtypes of USs (Gadducci 2011). In cases of CS, LMS and ESS, stage has been found to be an independent prognostic factor as regards survival (Chauveinc et al. 1999, Chan et al. 2008, Kapp et al. 2008, Nemani et al. 2008, Abeler et al. 2009, Gonzalez Bosquet et al. 2010).

Tumor necrosis

The presence of tumor cell necrosis has been independently associated with worse prognosis among patients with ESS (Abeler et al. 2009). This pathological feature has also been linked to prognosis of LMS patients (Ip and Cheung 2011), but the findings are inconsistent (Abeler et al. 2009).

Tumor size and myometrial invasion

Tumor size (cut-off values 50, 100 and 110mm) has been reported to be an independent prognostic factor as regard LMS and ESS (Nordal et al. 1996, Wu et al. 2006, Abeler et al. 2009, D'Angelo et al. 2011). In cases of CS and ESS, the depth of myometrial invasion has been found to be of prognostic relevance (mostly in univariate analysis) (Major et al. 1993, Marth et al. 1997, Bodner et al. 2001).

Bilateral salpingo-oophorectomy

The prognostic relevance of BSO has been assessed only among patients with LMS and ESS, who in general are younger than CS patients. The impact of oophorectomy on the survival of LMS patients aged less than 50 years has been reported in a few studies (Gadducci et al. 1996, Giuntoli et al. 2003, Kapp et al. 2008): preservation of the ovaries was not associated with negative survival in this subgroup of patients. On the other hand BSO is thought to be mandatory as regards ESS patients (Li et al. 2008, Gadducci 2011, Beck 2012). Some reports, however, have indicated that ovarian preservation has no negative influence on the survival of patients with early-stage ESS (Amant et al. 2007, Chan et al. 2008, Shah et al. 2008, Amant et al. 2009a).

Lymph node status and lymphadenectomy

The prognostic value of lymph node status and the LND in cases of different US subtypes is ambiguous (Gadducci 2011). In a study by Kokawa et al., LND was performed in 42% of patients with all US subtypes without any statistically significant survival benefit (Kokawa et al. 2006).

Carcinosarcoma patients with positive lymph node status at the time of primary surgery have shown both poorer survival (Galaal et al. 2009) and survival equal to that in lymph node negative patients (Gonzalez Bosquet et al. 2010). LND has been associated with improved overall survival in cases of stage I–III CS (Nemani et al. 2008). The lymph node count (< 11 lymph nodes versus ≥ 11) has been found to be associated with a risk of recurrence and with survival in stage I–II CS (Temkin et al. 2007). However, such an association (< 12 lymph nodes versus ≥ 12) was not seen in stage I–III CSs in SEER data (Nemani et al. 2008).

Kapp et al. reported that the 5-year disease-specific survival of patients with LMS was 26% in cases with lymph node metastases compared with 64.2% in patients without lymph node metastases ($p < 0.001$) in univariate analysis, but lymph node status was not associated with survival in multivariate analysis (Kapp et al. 2008). In other studies, LND has had no effect on the survival of LMS patients (Giuntoli et al. 2003, Sagae et al. 2004, Ayhan et al. 2009).

In 2008, Chan et al. reported that positive lymph node status at the time of surgery in cases of low- and high-grade ESS (n = 831) was associated with poorer survival, when looking at SEER data from 1988 to 2003 (Chan et al. 2008). In the same year, Shah et al. evaluated low- and high-grade ESSs (n = 970) independently in another SEER study and reported the opposite result among low-grade ESS patients (Shah et al. 2008). However, both groups of investigators concluded that LND had no impact on survival of ESS patients (Chan et al. 2008, Shah et al. 2008).

A summary of prognostic factors is presented in Table 11.

Table 11. Patient-, disease-, and treatment-related factors and their effects on prognosis of patients with uterine sarcoma (US)

Factor	Effect on prognosis	Subtype of US
Patient-related		
- Age	Older age → worse prognosis	All subtypes
- Ethnic background	Black race → worse prognosis	All subtypes
- Parity	0-parity → worse prognosis	ESS
Disease-related		
- Grade	Higher grade → worse prognosis	LMS
- Histology	See text	
- Immunohistochemistry	See text	
- LVI	LVI+ → worse prognosis	CS, LMS
- MI	Higher MI→ worse prognosis	LMS, ESS
- Stage	Higher stage → worse prognosis	All subtypes
- Tumor necrosis	Necrosis present → worse prognosis	LMS, ESS
- Tumor size	Larger tumor → worse prognosis	LMS, ESS
- Myometrial invasion	Deep myometrial invasion → worse prognosis	CS, ESS
Treatment-related		
- BSO*	BSO done → better prognosis	ESS**
	BSO done or not → no effect on prognosis	LMS#
- Lymph node status	LNM + → worse prognosis	CS
- Lymphadenectomy	LND done→ better prognosis	CS

CS = carcinosarcoma, LMS = leiomyosarcoma, ESS = endometrial stromal sarcoma, *with premenopausal patients, **no effect in early-stage ESS, #in early-stage LMS, LVI = lymphovascular space involvement, MI = mitotic index, BSO = bilateral salpingo-oophorectomy, LNM = lymph node metastasis

CONCLUSIONS OT THE LITERATURE REVIEW

Only a few etiological factors are known, and diagnostics, management and prognostic factors of these malignancies have been debated for years. The treatment recommendations of USs are mainly based on small phase II-III trials, retrospective studies, case-reports and case series. The roles of environmental and work-related factors in the induction of USs are mostly unknown and only one study on the risk of second primary cancers after US has been published. In the present study we tried to clarify these issues.

AIMS OF THE STUDY

The present study was undertaken to investigate the clinical behavior and prognostic factors of CS, LMS and ESS and elucidate epidemiological aspects of LMS and ESS.

Specific aims were to evaluate

1. trends in incidence and occupational variation in the risk of uterine LMS and ESS in the Nordic countries (I)

2. retrospectively the clinical data on uterine CS, LMS and ESS patients treated at Helsinki University Central Hospital between 1990 and 2001 (II)

3. immunohistochemical expression of ten oncoproteins in uterine CS, LMS and ESS and assess their relationship to patient survival (III)

4. the incidence of second primary malignancies after US (IV)

MATERIALS AND METHODS

These studies were undertaken during 2003–2011 at Helsinki University Central Hospital (HUCH) and approved by the Ethics Committee of the Department of Obstetrics and Gynecology, and the head of the Department of Obstetrics and Gynecology, and with the permission of the Ministry of Social Affairs and Health. Studies I and IV have been done in cooperation with all Nordic Cancer Registries and International Agency for Research and Cancer (IARC).

STUDY MATERIAL

The study material is summarized in Table 12.

Table 12. Study material

Study	All cases, *n*	CS, *n*	LMS, *n*	ESS, *n*	Study period/ location	Source of material
I	1913	NR	1184	729	1978–2007	NORDCAN database
			373	263	Finland	
			352	194	Denmark	
			26	10	Iceland	
			433	262	Norway	
I	1671	NR	1163	508		NOCCA database #
		NR	494	219	1971–2005, Finland	
		NR	388	130	1961–2003, Norway	
		NR	281	159	1993–2005, Sweden	
II	100	40	39	21	1990–2001, Finland	Patient registry of the Department of Obstetrics and Gynecology, HUCH
III	65	28	28	9	1990–2001, Finland	Patient registry of the Department of Obstetrics and Gynecology, HUCH
IV	8606	4342*	3507	757	1943–2000, ##	Thirteen cancer registries ##

NR = not reported, NOCCA = Nordic Occupational Cancer Study, HUCH = Helsinki University Central Hospital, * Other uterine sarcomas, # Data includes women aged 30–64 years at population censuses of 1960, 1970, 1980 or 1990, ## Finland, Denmark, Sweden, Norway, Iceland, Scotland, Spain, Slovenia, Canada (three centers), Australia and Singapore

Study I

In this study the incidences of uterine LMS (n = 1184) and ESS (n = 729) were calculated for five-year periods from 1978–1982 to 2003–2007 and for five-year age groups by means of the NORDCAN database (www.ancr.nu; (Engholm et al. 2010b)), which includes detailed information on cancer incidence, mortality and prevalence in each of the Nordic countries. Incidence rates for the US categories could not be calculated for Sweden.

Occupational variation in the risks of uterine LMS and ESS was analyzed from the Nordic Occupational Cancer Study (NOCCA) database. This cohort comprised 6.4 million women aged 30–64 years at population censuses of 1960, 1970, 1980 or 1990: 1.7 million in Finland, 1.3 million in Norway and 3.4 million in Sweden (Pukkala et al. 2009). The follow-up periods concerning cancer incidence were 1971–2005 in Finland, 1961–2003 in Norway and 1993–2005 in Sweden. During the follow-up periods, 1163 LMS and 508 ESS cases were detected in Finland, Norway and Sweden. The information on the occupation of each person was provided via free text in self-administered questionnaires: it was then centrally coded and computerized in the censuses of each country. Concerning NOCCA data, occupations were reclassified into 53 categories and one group of economically inactive persons (Table 13, (Pukkala et al. 2009)).

Table 13. Occupational categories used in NOCCA

1. Technical workers etc	14.Sales agents	27.Smelting workers	39.Beverage workers	49. Chimney sweeps
2. Laboratory assistants	15.Shop workers	28.Mechanics	40.Tobacco workers	50. Hairdressers
3. Physicians	16.Farmers	29.Plumbers	41.Glass makers etc	51. Launderers
4. Dentists	17.Gardeners	30.Welders	42.Packers	52.Military personnel
5. Nurses	18.Fishermen	31.Electrical workers	43.Engine operators	53."Other workers"
6. Assistant nurses	19.Forestry workers	32.Woodworkers	44.Public safety workers	54.Economically inactive*
7. "Other health workers"	20.Miners and quarry workers	33.Painters	45.Cooks and stewards	
8. Teachers	21.Seamen	34."Other construction workers"	46.Domestic assistants	
9.Religious workers etc	22.Transport workers	35.Bricklayers	47.Waiters	
10.Artistic workers	23.Drivers	36.Printers	48.Building caretakers	
11.Journalists	24.Postal workers	37.Chemical process workers		
12.Administrators	25.Textile workers	38.Food workers		
13.Clerical workers	26.Shoe and leather workers			

* This group includes housewives, early pensioners, students and persons on social support.

Studies II and III

For these two studies, medical records were reviewed and data collected concerning all uterine sarcomas (n = 100) treated during a 12-year period (1990 to 2001) at HUCH. The head of the Department of Obstetrics and Gynecology at HUCH approved the study design (chart review) and the Ethics Board of HUCH approved the IHC analysis of tissue samples. Follow-up data was acquired from district hospitals with approval from the Ministry of Social Affairs and Health.

For Study II, all cases of uterine CS (n = 40), LMS (n = 39) and ESS (n = 21) were included. A pathologist at our institution made the diagnosis of US either at the time of primary operation or on evaluation of tumor slides. Our pathologist (R.B.) reviewed the histopathology slides in terms of two level grading systems in Study II. CS was considered a high-grade tumor (Tavassoli and Devilee 2003, Abeler et al. 2009) and LMS was defined as low-grade or high-grade depending on cellularity, cellular atypia, mitotic activity, vascular space involvement and necrosis (Studies II and III) (Tavassoli and Devilee 2003). The main criteria for grading of LMS were tumor necrosis and mitotic count (low-grade tumors: significant atypia, no tumor necrosis and mitotic count < 15–20/10 HPFs, and high-grade tumors: significant atypia, tumor necrosis and/or mitotic count > 15–20/10 HPFs). Traditionally, ESS has been divided into low- and high-grade tumors, mainly according to mitotic activity and this grading system was used in Study II.

For Study III, there was sufficient histological material available for IHC analysis and slide review in 67 cases. In the study, one representative block per case was selected for immunohistochemistry. Even though the tumor slides had been assessed in a two-grade system in Study II, the diagnosis of four high-grade ESS tumors changed in re-evaluation for Study III. One of the tumors turned out to be adenosarcoma, one was an undifferentiated endometrial sarcoma, and there were two carcinosarcomas. The low-grade tumor definition of ESS was applied in study III (Tavassoli and Devilee 2003, Abeler et al. 2009). For final analysis, 65 uterine sarcomas (28 CSs, 28 LMSs and 9 ESSs) were chosen.

Times to recurrence (Study II), progression (Study II), death (Study II and III) and latest contact (Studies II and III) were noted. The cut-off point for survival analysis was December 31, 2005 in Study II and April 30, 2008 in Study III. Stage was defined by means of the modified FIGO criteria for endometrial adenocarcinoma (International Federation of Gynecology and Obstetrics 2006).

Study IV

In this multi-center study of second primary cancers, data was collected from 13 cancer registries – in Finland, Denmark, Sweden, Norway, Iceland, Scotland, Spain, Slovenia, Canada (three centers), Australia and Singapore coordinated by IARC. The cohort comprised 8606 women with a first US (LMS n = 3507, ESS n = 757 and other or undefined US n = 4342) and represented 56823 person-years of follow-up. The majority of USs was from Europe (79%).

The category of other or undefined uterine sarcomas included carcinosarcomas, adenosarcomas, undifferentiated endometrial sarcomas and other uterine sarcomas. No treatment data for US were available.

METHODS

Statistical analyses

Studies I and IV

In Study I, standardized incidence ratios (SIRs) for LMS and ESS by country and occupational category were computed. The SIR is the ratio of observed (Obs) and expected (Exp) number of cancer cases. The expected numbers were based on the cancer incidence rates of the entire national female population. For SIRs, exact 95% confidence intervals were calculated assuming a Poisson distribution of the observed cases. SIRs for US could not be calculated for Denmark and Iceland.

In Study IV all cases of US were followed up in connetion with second primary cancer from the date of first diagnosis (1943–2000), to the date of second primary cancer (1943–2000), the date of death, the date of migration or the end of follow-up (1992–2000). The number of second primary cancers observed was compared with the expected number of cancers calculated from accumulated person-years among females with first US, specific for each cancer registry, and five-year age and calendar-periods and respective primary incidence rates in the national female populations (excluding other cancers of female genital organs). The SIRs were stratified for time since US diagnosis, for calendar-period of US and for age at US diagnosis. Poisson regression analyses were carried out for selected cancer sites to quantify the independent risk ratios (RRs) related to age and calendar period at US diagnosis and time since US diagnosis.

Studies II and III

In both studies, survival curves were generated by using the Kaplan–Meier method, and median survival times with 95% confidence intervals (95% CIs) were given. Comparison of survival curves between groups (Study II) and between negative and positive marker status (Study III) was performed using the log-rank test. Those variables found to be statistically significant in univariate analysis in Study II were examined by multivariate analysis using Cox´s proportional hazards regression model: hazard ratios and their 95% CIs were reported. In Study III, survival analyses were carried out separately for each uterine sarcoma type, but because of the small sample size, results were not reported for ESS.

For Study III, associations between the type of uterine sarcoma and IHC markers were evaluated using cross-tabulation and Fisher´s exact χ^2 -test. Androgen receptors and c-kit were not tested because all AR staining results were negative, and there were only two cases of positive c-kit staining.

Statistical analysis was performed using SPSS statistical software for Windows versions 13.0 and 16.0 (SPSS INC., Chicago, IL). A p value of less than 0.05 was considered statistically significant for all tests.

Immunohistochemical analysis

For ICH in Study III, formalin-fixed, paraffin-embedded tissue samples of all uterine sarcomas were used. Staining was performed by using a LabVision immunostainer (LabVision, CA, USA). Antigen retrieval was carried out in Tris-EDTA buffer, pH 9.0. It was done in a microwave oven for 24 minutes at 900 watts, cooling for 20 minutes at room temperature. The IHC studies involved a polymer-based detection system (Envision, K5007, DakoCytomation) with diaminobenzidine chromogen. The primary antibodies used in Study III are listed in Table 14.

Table 14. Antibodies used for immunohistochemical analysis in Study III

Antibody	Dilution	Manufacturer / product number / clone
MIB1*	1:200	DakoCytomation / (M7240) / MIB-1
p53	1:150	DakoCytomation / (M 7001) / DO-7
CD10	1:20	Novocastra / (NCL-CD10-270) / 56C6
CD44	1:50	DakoCytomation / (M7082) / DF1485
Desmin	1:100	DakoCytomation / (M0760) / D33
Actin	1:100	DakoCytomation / (M0760) / 1A4
Estrogen receptor-α	1:50	Novocastra / (NCL-ER-6F11) / 6F11
Androgen receptor	1:25	Novocastra / (NCL-AR-318) / AR27
Progesterone receptor	1:200	DakoCytomation / (M3569) / PgR636
c-kit	1:300	DakoCytomation / (A4502) / polyclonal

*Antibody against Ki-67

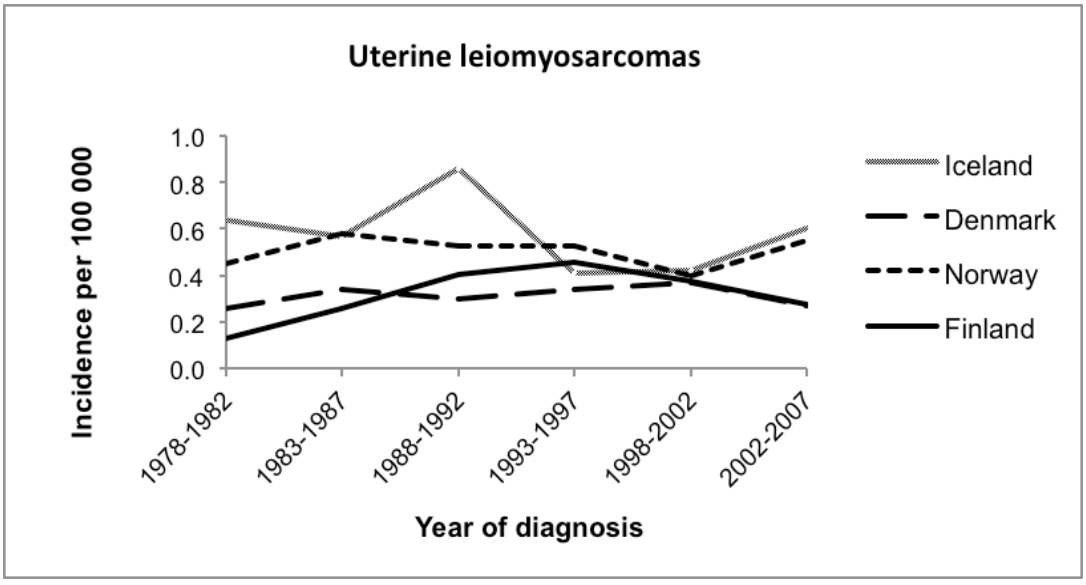
Immunoreactivity was scored semiquantitatively. The intensity of the immunoreaction was rated as zero to three (0 = cannot be assessed, 1= negative, 2 = positive with regard to p53, c-KIT, CD10, CD44, desmin, SMA, AR, ER-α and PR; 0 = cannot be assessed, 1 = < 5% positive, 2 = 5–50% positive, 3 = > 50% positive with regard to Ki-67). Two investigators (R.B. and R.K-K.) blinded to the clinical data came to a consensus of opinion concerning the stained slides.

RESULTS

INCIDENCE AND OCCUPATIONAL RISKS OF LMS AND ESS IN NORDIC COUNTRIES

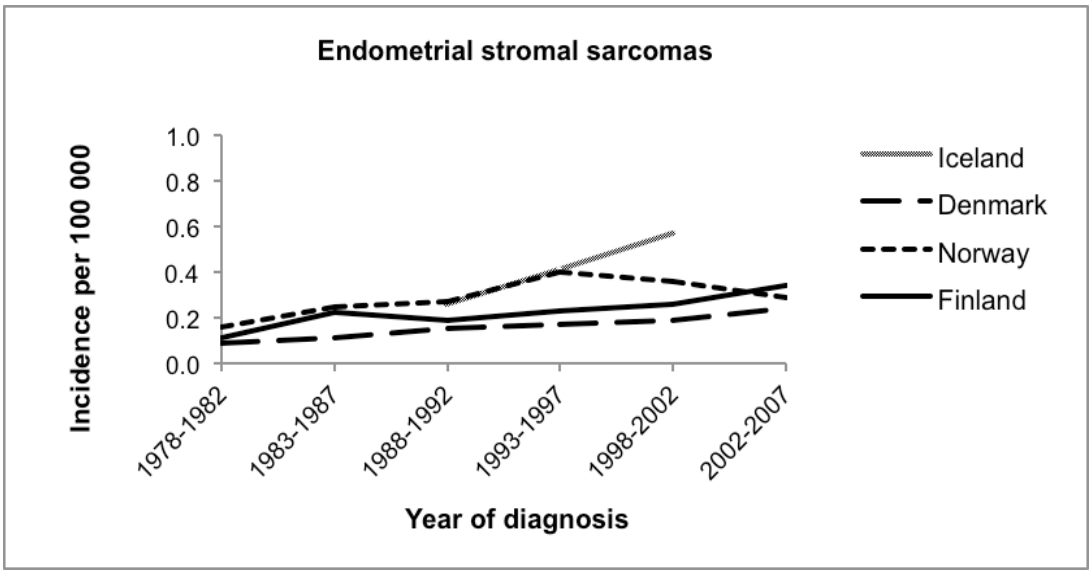
The incidence of LMS was relatively stabile over the years in all four countries (Figure 5). The rates in Iceland and Norway were about 0.5 per 100,000, slightly higher than in Denmark and Finland. The rates for ESS were about 0.2 per 100,000, but with some suggestion of an increase (Figure 6). The incidence of LMS was highest in the age groups of 45–59 years (Figure 7). The incidence rates of ESS were constant from the age group of 45–49 years onwards.

Figure 5. Incidence of uterine leiomyosarcoma in Iceland, Denmark, Finland and Norway, by 5-year periods; adjusted for age to the World Standard Population*



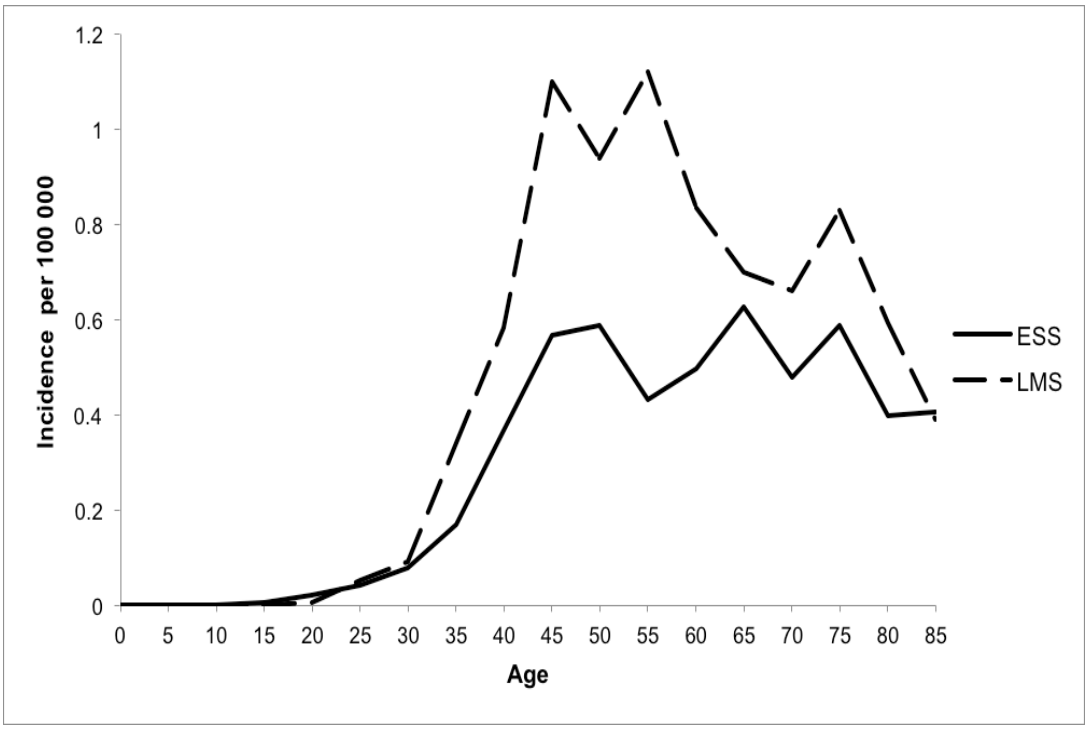
*Tabulation based on NORDCAN data (Engholm et al. 2010b)

Figure 6. Incidence of endometrial stromal sarcoma in Iceland, Denmark, Finland and Norway, by 5-year periods; adjusted for age to the World Standard Population*



*Tabulation based on NORDCAN data (Engholm et al. 2010b)

Figure 7. Age-specific incidence rates of uterine leiomyosarcoma and endometrial stromal sarcoma in Iceland, Denmark, Finland and Norway from 1978 to 2007*



LMS = leiomyosarcoma, ESS = endometrial stromal sarcoma
*Tabulation based on NORDCAN data (Engholm et al. 2010b)

In the NOCCA study, including Finland, Norway and Sweden, the occupational groups with significantly increased SIRs of LMS were shoe and leather workers, farmers and teachers. The only occupational group with a significantly decreased SIR was domestic assistants (Table 15). For ESS, no occupations with elevated SIRs were observed.

Table 15. Observed numbers (Obs) and statistically significantly increased or decreased standardized incidence ratios (SIRs, $p < 0.05$) of uterine leiomyosarcoma among women in Finland (1971–2005), Norway (1961–2003) and Sweden (1993–2005), by occupational category

Occupational category	Finland		Norway		Sweden		Total			
	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	95%CI	
Shoe and leather workers	3	1.43	3	4.55	2	6.16	8	2.59	1.12	— 5.11
Farmers	22	1.73	21	1.56	2	1.19	45	1.62	1.18	— 2.17
Teachers	27	1.57	13	0.99	26	1.49	66	1.38	1.07	— 1.76
Domestic assistants	7	0.71	9	0.73	7	0.51	23	0.64	0.41	— 0.96
All categories	494	1.00	388	1.00	281	1.00	1163	1.00	Ref.	

95% confidence intervals (95% CI) of the SIR are given for the total of the three countries.

CLINICAL AND PROGNOSTIC FACTORS AND SURVIVAL IN CASES OF CS, LMS AND ESS

Clinical findings

Patient demographics and clinical findings are summarized in Table 16.

Table 16. Patient characteristics as regards different types of uterine sarcoma

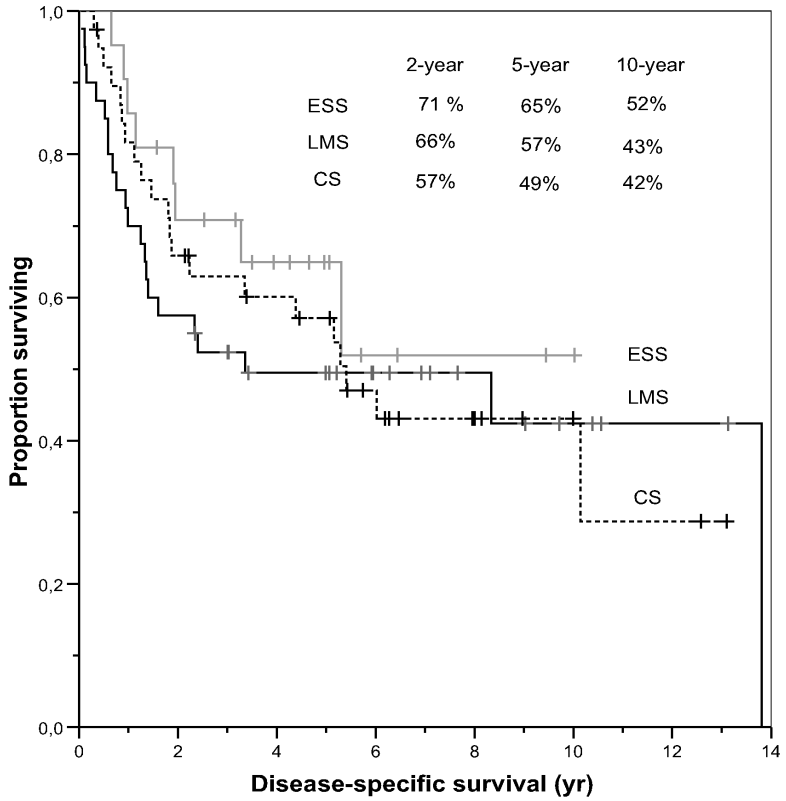
Characteristic	CS (*n* = 40)	LMS (*n* = 39)	ESS (*n* = 21)	All (*n* = 100)
Median age, years (range)	65 (42–89)	52 (27–86)	52 (37–83)	60 (27–89)
Stage				
- I	16	23	15	54
- II	3	2	0	5
- III	15	9	4	28
- IV	6	3	2	11
- Not known	0	2	0	2
Grade				
- Low-grade	0	24	13	37
- High-grade	40	15	8	63
Primary operation	39	38	21	98
- Hysterectomy	36	33	21	90
- Other operation	3	5	0	8
BSO done	38	33	18	89
Lymph node evaluation	24	15	13	52
- Not done	16	24	8	48
- Only biopsies	11	8	4	23
- Done	13	7	9	29
LNM	6	0	1	7
Adjuvant CT (%)	13 (33%)	21 (54%)	7 (33%)	41
- CEP	13	2	7	22
- EI	0	19	0	19
Adjuvant RT (%)	28 (70%)	5 (13%)	18 (86%)	51
- Pelvic	3	4	3	10
- Pelvic + BT	15	1	9	25
- BT	10	0	6	16
Response (%)				
- Complete response	33 (82%)	29 (74%)	18 (86%)	80
- Partial response	1 (3%)	3 (8%)	0 (0%)	4
- Progressive disease	6 (15%)	7 (18%)	3 (14%)	16
Recurrence (%)	16 (48%)	16 (55%)	8 (44%)	40 (50%)

BSO = bilateral salpingo-oophorectomy, LNM = lymph node metastasis, CT = chemotherapy, RT = radiotherapy, BT = brachytherapy, CEP = cisplatin + epirubicin + cyclophosphamide, EI = etoposide + ifosfamide, Values are given as number of observations (*n*), if not otherwise stated.

Survival

The median disease-specific survival time for all patients was 65 months (95%CI 22–108 months). The 2-, 5- and 10-year overall survival rates were 62%, 51% and 38% and disease-specific survival rates were 64%, 56% and 44%. Five-year survival in cases of ESS (65%) was better than in cases of LMS (57%) and CS (49%), but when comparing survival times there were no statistically significant differences between histological types ($p = 0.613$, Figure 8). Lower stage ($p < 0.001$), lower grade ($p = 0.009$), younger age ($p < 0.001$) and small tumor size ($p = 0.050$) were all associated with statistically significantly improved disease-specific survival in univariate analysis. Delivery status was also associated with disease-specific survival ($p = 0.001$); those having more deliveries had a worse disease-specific survival.

Figure 8. Disease-specific survival as regards uterine carcinosarcoma, leiomyosarcoma and endometrial stromal sarcoma (Kaplan–Meier analysis)



The median time to recurrence was 14 months (range 4–116 months) for all types of relapsed uterine sarcomas, 11 months (range 4–80 months) for CSs, 19 months (range 6–116 months) for LMSs and 15 months (range 4-32 months) for ESSs. As calculated for relapsing patients only, the median progression-free survival was 8 months (range 2–82 months).

In multivariate analysis, stage, tumor size and delivery status were found to have independent influences on both overall and disease-specific survival, and age only on overall survival (Table 17).

Table 17. Multivariate analysis: overall and disease-specific survival in Study II (n = 64)

Variable	**Overall survival Hazard ratio (95%CI)**	***p***	**Disease-specific survival Hazard ratio (95%CI)**	***p***
Age (years)		0.016		0.100
< 50	1.0 (ref.)		1.0 (ref.)	
50–59	2.6 (0.6–11.8)		2.5 (0.6–11.7)	
60–69	2.2 (0.5–10.2)		2.3 (0.5–11.3)	
70–79	6.9 (1.1–41.5)		7.6 (1.2–47.9)	
80–	17.0 (2.6–109.5)		11.1 (1.5–82.7)	
Stage		< 0.001		< 0.001
I	1.0 (ref.)		1.0 (ref.)	
II	4.4 (0.6–29.5)		3.7 (0.5–30.0)	
III	4.9 (1.7–14.3)		3.5 (1.0–11.4)	
IV	38.2 (9.4–155.5)		37.6 (8.4–169.3)	
Tumor size		0.001		0.001
< 5 cm	1.0 (ref.)		1.0 (ref.)	
5–10 cm	2.4 (0.9–6.0)		2.6 (1.0–7.1)	
> 10 cm	7.8 (2.5–24.0)		10.5 (3.1–35.1)	
Delivery status		0.009		0.005
no pregnancies	1.0 (ref.)		1.0 (ref.)	
one delivery	1.8 (0.4–7.4)		2.3 (0.5–11.2)	
two deliveries	1.5 (0.4–5.2)		2.0 (0.5–7.5)	
three deliveries	11.4 (2.7–47.8)		15.5 (3.4–69.7)	
≥ four deliveries	1.4 (0.3–5.6)		1.3 (0.3–6.0)	

CI = confidence interval, ref. = reference category

IMMUNOHISTOCHEMICAL MARKERS AND THEIR PROGNOSTIC SIGNIFICANCE IN CASES OF UTERINE CS, LMS AND ESS

Immunohistochemical analysis

The expression of Ki-67, p53, CD10, CD44, desmin, SMA, ER-α, AR, PR and c-KIT was evaluated by immunohistochemistry. All cases were AR-negative, and c-kit was weakly positive in only two cases of ESS. Smooth muscle actin was statistically significantly associated with the type of sarcoma ($p = 0.003$); in LMS, more cases stained positively (78%) than in other sarcoma types. Associations between Ki-67, desmin and PR *vs.* type of sarcoma were of borderline significance. In IHC analysis, there were a few cases that could not be evaluated (two with regard to desmin and SMA, three with regard to Ki-67, p53, CD10, CD 44 and PR, and five with regard to ER-α). The expression of IHC markers (except AR and c-kit) according to the type of uterine sarcoma is summarized in Table 18.

Table 18. Immunohistochemical (IHC) profiles according to uterine sarcoma subtype

IHC marker	CS *n* = 26–28* *n* (%)	LMS *n* = 26–28* *n* (%)	ESS *n* = 8–9* *n* (%)	All *n (%)*	*p*
Ki-67					0.069
<5% pos	3 (11)	9 (33)	3 (37,5)	15 (24)	
5–50% pos	17 (63)	15 (56)	2 (25)	34 (55)	
>50% pos	7 (26)	3 (11)	3 (37,5)	13 (21)	
p53					0.785
neg	19 (70)	20 (74)	7 (88)	46 (74)	
pos	8 (30)	7 (26)	1 (12)	16 (26)	
CD10					0.532
neg	12 (44)	16 (59)	3(38)	31 (50)	
pos	15 (56)	11 (41)	5 (62)	31 (50)	
CD44					0.136
neg	11 (41)	17 (63)	6 (75)	34 (55)	
pos	16 (59)	10 (37)	2 (25)	28 (45)	
Desmin					0.075
neg	19 (68)	11 (41)	6 (75)	36 (57)	
pos	9 (32)	16 (59)	2 (25)	27 (43)	
SMA					0.003
neg	17 (61)	6 (22)	6 (75)	29 (46)	
pos	11 (39)	21 (78)	2 (25)	34 (54)	
Estrogen receptor-α					0.258
neg	20 (77)	15 (58)	4 (50)	39 (65)	
pos	6 (23)	11 (42)	4 (50)	21 (35)	
Progesterone receptor					0.084
neg	20 (74)	12 (44)	4 (50)	36 (58)	
pos	7 (26)	15 (56)	4 (50)	26 (42)	

CS = carcinosarcoma, LMS = leiomyosarcoma, ESS = endometrial stromal sarcoma, SMA = smooth muscle actin, *The number of cases varies because in each group there were instances of IHC staining that could not be analyzed.

Survival

The median disease-specific survival time for all patients was 66 months (95% CI 0–152 months). ER-α- and PR-positivity were associated with statistically significantly better disease-specific survival times in cases of LMS (Figures 9 and 10). Oncoprotein p53 overexpression was associated adversely with the survival of LMS patients (p = 0.011). Strong Ki-67 expression in cases of CS was associated with a tendency to show worse disease-specific survival (p = 0.055, Table 19). No relationship was found between the markers CD10, CD44, desmin and SMA, and survival.

Table 19. Median disease-specific survival times according to IHC staining intensity of Ki-67, p53, estrogen receptor-α (ER-α) and progesterone receptor (PR) in cases of uterine carcinosarcoma (CS) and leiomyosarcoma (LMS)

Variable	**CS**	**Median survival time, months (95%CI)**		**LMS**	**Median survival time, months (95%CI)**	
	n		***p***	***n***		***p***
Ki-67			0.055			0.188
<5% pos	3	41 (0-92)		9	*	
5–50% pos	17	168 (0-349)		15	64 (33-96)	
>50% pos	7	7 (7-8)		3	27 (0-61)	
p53			0.746			0.011
neg	19	23 (0-57)		20	123 (#)	
pos	8	29 (0-176)		7	11 (3-20)	
ER-α			0.482			0.005
neg	20	20 (6-33)		15	41 (1-80)	
pos	6	102 (0-284)		11	*	
PR			0.896			0.012
neg	20	20 (6-33)		12	53 (16-91)	
pos	7	41 (0-104)		15	*	

CI = confidence interval, *Cannot be defined, because more than 50% were alive at the cut-off point for survival analysis, #Cannot be calculated.

Figure 9. Disease-specific survival of patients with uterine leiomyosarcoma according to estrogen receptor-α status in Study III

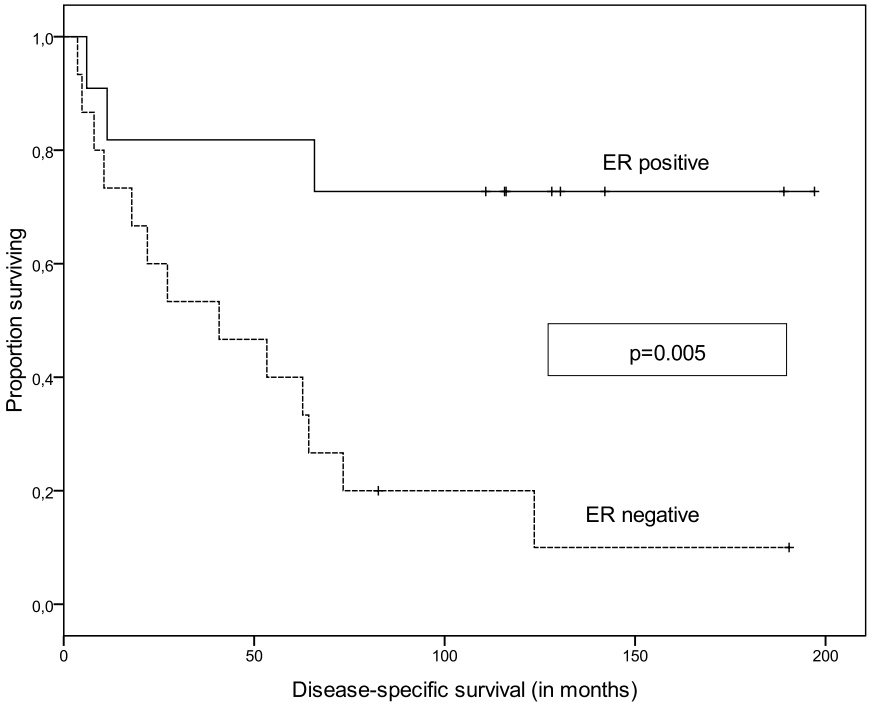
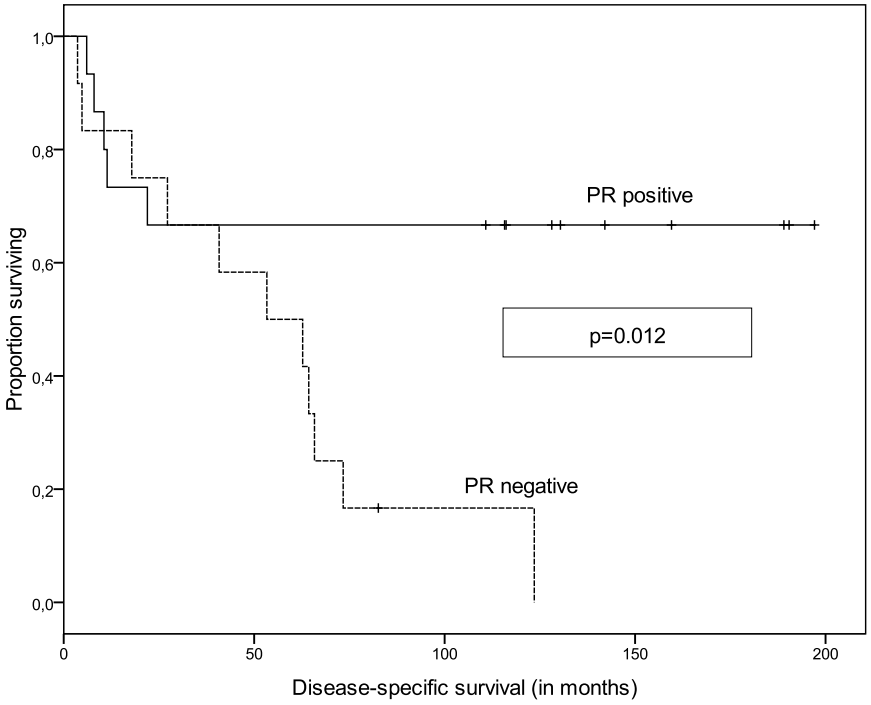


Figure 10. Disease-specific survival of patients with uterine leiomyosarcoma according to progesterone receptor status in Study III



SECOND PRIMARY MALIGNANCIES AFTER UTERINE SARCOMA

There were 499 cancer cases observed after first US: 215 after LMS, 36 after ESS and 248 after other or undefined US. The SIR of a second primary cancer at all sites combined (excluding female genital organs) after a US of any type was 1.26 (95%CI 1.16–1.38). Significantly elevated SIRs were seen in connection with cancers of the mouth and pharynx, colorectum, lung, breast, urinary bladder, kidney, and thyroid gland, and soft tissue sarcoma (Table 20). There were no second cancers with significantly reduced SIRs after US diagnosis.

Significantly elevated SIRs after first uterine LMS were seen for all sites combined, for rectum and lung cancer, and for soft tissue sarcoma (Table 21). In the ESS subgroup, none of the SIRs of second primary cancer reached statistical significance. In the group of patients with other or undefined USs, SIRs were elevated for colorectal, lung, urinary bladder, kidney and thyroid cancer (Table 22).

Table 20. Second primary cancer sites with statistically significantly elevated standardized incidence ratios (SIRs) among 8 606 women with a first primary uterine sarcoma

Cancer site (ICD-9)	Observed*	SIR	95%CI
All malignant (140-208)**	499	1.26	1.16–1.38
Soft tissue sarcoma (171)	10	5.23	2.51–9.62
Thyroid gland (193)	12	2.74	1.42–4.79
Mouth and pharynx (140-149)	13	2.16	1.15–3.69
Kidney (189, excluding 189.3-4)	21	2.00	1.24–3.06
Urinary bladder (188, 189.3-4)	17	1.74	1.02–2.79
Lung (162)	48	1.73	1.27–2.29
Colorectal (153,154)	86	1.60	1.28–1.98
Breast (174)	132	1.25	1.05–1.49

*Observed numbers of subsequent primary cancer cases, CI = confidence interval, **Excluding other cancers of female genital organs

Table 21. Second primary cancer sites with statistically significantly elevated standardized incidence ratios (SIRs) among 3 507 women with a first primary uterine leiomyosarcoma

Cancer sites (ICD-9)	Observed*	SIR	95%CI
All malignant (140–208)**	215	1.28	1.12–1.46
Soft tissue sarcoma (171)	8	8.79	3.80–17.3
Colorectal (153,154)	38	1.85	1.31–2.53
Lung (162)	19	1.73	1.04–2.70

*Observed numbers of subsequent primary cancer cases, CI = confidence interval, **Excluding other cancers of female genital organs

Table 22. Second primary cancer sites with statistically significantly elevated standardized incidence ratios (SIRs) among 4 342 women with a first primary other uterine sarcoma

Cancer sites (ICD-9)	Observed*	SIR	95%CI
All malignant (140–208)**	248	1.24	1.09–1.40
Thyroid gland (193)	7	4.05	1.63–8.34
Kidney (189, excluding 189.3–4)	12	2.28	1.18–3.99
Bladder (188, 189.3, 189.4)	11	2.04	1.02–3.64
Lung (162)	25	1.71	1.11–2.52
Colorectal (153, 154)	43	1.46	1.06–1.97

*Observed numbers of subsequent primary cancer cases, CI = confidence interval, **Excluding other cancers of female genital organs

The SIR for second cancer (all sites combined) was highest if age at US diagnosis was less than 50 years, the year of US diagnosis was 1975–1983 or if the time since US diagnosis was 10 or more years. For breast cancer, SIRs were highest if the age at US diagnosis was 60 years or more. The result was the same in multivariate analysis, adjusting for the year of US diagnosis and time since US diagnosis. For colorectal cancer, SIRs increased with increasing time since diagnosis of US, but none of the variables had significant independent effects on risk in multivariate analysis. However, there was still a suggestive trend towards an increasing risk of colorectal cancer with increasing time since diagnosis of US. For kidney cancer, SIRs were highest if the age at US diagnosis was less than 50 years and the time since diagnosis was less than one year. The same pattern as regards age and time since US diagnosis was detected in multivariate analysis. For the other sites, the numbers of cases were too small to allow multivariate analysis. The data is summarized in Tables 23 and 24.

Table 23. Observed numbers and standardized incidence ratios for second primary cancers at selected sites among 8 606 women with a first uterine sarcoma, by age and calendar period at uterine sarcoma diagnosis and by time since uterine sarcoma diagnosis

Factor	Age at US diagnosis			Year of US diagnosis				Years since US diagnosis			
	< 50	50–59	≥ 60	< 1975	1975–1983	1984–1990	1991 +	≤1	1–4	5–9	10+
All malignant											
Obs	186	136	177	223	144	86	46	45	121	93	240
SIR	1.36	1.20	1.23	1.25	1.45	1.23	1.00	1.00	1.26	1.21	1.36
95%CI	1.17–1.56	1.01–1.41	1.10–1.42	1.10–1.42	1.22–1.70	0.98–1.51	0.73–1.33	0.73–1.34	1.04–1.49	0.98–1.48	1.20–1.54
Colorectal											
Obs	29	25	32	41	27	12	6	5	16	17	48
SIR	1.91	1.64	1.35	1.64	2.01	1.30	1.01	0.84	1.29	1.71	1.98
95%CI	1.28–2.75	1.06–2.42	0.94–1.94	1.18–2.23	1.32–2.92	0.67–2.27	0.37–2.19	0.27–1.95	0.74–2.10	1.00–2.74	1.39–2.50
Lung											
Obs	14	13	21	13	16	12	7	5	13	9	21
SIR	1.61	1.57	1.94	1.26	2.09	2.03	1.79	1.57	1.94	1.69	1.67
95%CI	0.88–2.70	0.84–2.69	1.20–2.97	0.67–2.16	1.19–3.39	1.05–3.54	0.72–3.69	0.51–3.67	1.03–3.32	0.77–3.21	1.03–2.55
Breast											
Obs	53	32	47	59	36	29	8	8	35	29	60
SIR	1.20	1.04	1.55	1.31	1.33	1.48	0.60	0.67	1.29	1.35	1.35
95%CI	0.90–1.57	0.71–1.47	1.14–2.07	1.00–1.69	0.93–1.84	0.99–2.12	0.26–1.18	0.29–1.31	0.90–1.80	0.90–1.93	1.03–1.73
Kidney											
Obs	10	7	4	10	6	1	4	6	5	2	8
SIR	2.93	2.19	1.03	1.96	2.38	0.57	3.64	5.43	2.11	1.03	1.58
95%CI	1.40–5.39	0.88–4.52	0.28–2.65	0.94-3.60	0.87–5.18	0.01–3.20	0.99–9.32	1.99–11.8	0.69–4.93	0.13–3.74	0.68–3.11

US = uterine sarcoma, Obs = observed, SIR = standardized incidence ratio, CI = confidence interval

Table 24. Risk ratios for second primary cancers in selected sites among 8 606 women with a first uterine sarcoma, by age and calendar period at uterine sarcoma diagnosis, and by time since uterine sarcoma diagnosis

Factor	Breast		Colorectal		Lung		Kidney	
	RR (95%CI)	*p* trend	RR (95%CI)	*p* trend	RR (95%CI)	*p* trend	RR (95%CI)	*p* trend
Age at US diagnosis								
- <50	0.63 (0.41–0.98)		1.20 (0.66–2.17)		0.94 (0.42–2.11)		7.03 (1.89–26.2)	
- 50-59	0.58 (0.36–0.93)		1.04 (0.59–1.83)		0.84 (0.40–1.76)		3.76 (1.04–13.6)	
- ≥60	1.00 (ref.)	**0.040**	1.00 (ref.)	0.644	1.00 (ref.)	0.758	1.00 (ref.)	**0.004**
Year of US diagnosis								
- <1975	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
- 1975-1983	0.95 (0.62–1.47)		1.40 (0.83–2.35)		1.76 (0.80–3.84)		1.33 (0.46–3.90)	
- 1984-1990	1.04 (0.63–1.47)		1.02 (0.49–2.14)		1.82 (0.70–4.75)		0.29 (0.03–2.49)	
- >1990	0.45 (0.20–1.01)	0.288	0.94 (0.35–2.53)	0.787	1.65 (0.51–5.29)	0.249	1.32 (0.33–5.26)	0.993
Years since US diagnosis								
- <1	0.51 (0.24–1.10)		0.66 (0.24–1.82)		0.80 (0.28–2.25)		3.18 (0.95–10.6)	
- 1-4	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
- 5-9	0.97 (0.59–1.61)		1.25 (0.62–2.53)		0.91 (0.38–2.22)		0.38 (0.07–2.02)	
- ≥10	1.05 (0.65–1.70)	0.333	1.36 (0.69–2.69)	0.182	1.18 (0.48–2.89)	0.471	0.34 (0.10–1.18)	**0.018**

RR = risk ratio, US = uterine sarcoma, CI = confidence interval, ref. = reference category

DISCUSSION

Our study showed relatively constant incidence trends of ESS and LMS in Nordic countries and in connection with certain occupations, a significantly elevated incidence of LMS (I). Our survival rates in cases of US were comparable or even better than in earlier studies and we noticed that higher parity could have a negative influence on survival in cases of US (II). In IHC analysis, the expression of ER-α, PR and p53 was associated with survival of LMS patients (III). We demonstrated an increased risk of second primary malignancies following a diagnosis of US (IV).

Strengths and limitations of the present study

We had a great opportunity to use the NORDCAN and NOCCA databases, to view trends in incidences and occupational risks of LMS and ESS in Nordic countries, and in Study IV to analyze second primary malignancies after first primary US in an international multicenter trial coordinated by IARC. Both NORDCAN and NOCCA offered data on large cohorts of LMS and ESS patients, even thought we could not calculate the incidence rates for Sweden and SIRs for occupational category for Denmark and Iceland. An extra advantage of large cohorts is long follow-up times. In retrospective studies (II+III) we had a relatively large sample size from one institution when comparing with earlier, similar studies on USs. To the best of our knowledge, this is the first time that the incidence and occupational risks of uterine LMS and ESS have been evaluated in the Nordic countries, and it was the largest multinational US patient cohort ever collected for a second primary malignancy study. Although the results of retrospective studies should always be interpreted with caution, our data on survival and prognostic factors are comparable with those in earlier retrospective studies on USs.

A limitation of Studies I and IV is the lack of individual data on risk factors and treatment methods, and results should be interpreted with caution. There is always the possibility of coding problems when data is collected from 13 cancer registries, although a conservative coding principle was used. The retrospective study design and the small number of patients in different US subgroups are limitations of Studies II and III, but an attempt has been made to take these factors into account in assessing and discussing the results. For the reader it is important to know that we have used the term adjuvant therapy in connection with all patients who have been treated by means of first-line therapy. Comparison of IHC analyses in different studies is also problematic because variations in staining may be the result of many factors and the cut-off values concerning staining can radically differ. In addition the analysis of slides is a subjective method.

The classification of USs changed during this research project. Uterine CS has been reclassified as a metaplastic carcinoma of endometrial origin (McCluggage 2002c) and ESS as a low-grade malignancy (Tavassoli and Devilee 2003). Undifferentiated endometrial sarcoma has replaced the term high-grade ESS. However, CS was selected in two retrospective studies (II + III) because of the study design and for historical reasons. In Study II, the group of "high-grade ESS" remained, but after re-evaluation of pathological slides for Study III, only low-grade ESS existed in the ESS group.

Trends in incidences of uterine LMS and ESS in Nordic countries

Very few studies exist on the incidence of USs and its change over the years (Harlow et al. 1986, Nordal and Thoresen 1997). In our study period, the incidence rates of both LMS and ESS were relatively similar and constant in four Nordic Countries. Age-specific incidences of LMS and ESS increased up to the age groups around menopause, but decreased after the age of 60 in cases of LMS. Using the SEER data, Harlow et al. published a demographic study of 1452 USs in the United States (1973–1981): the overall annual incidence of all cases of US was 1.7, for that of CS 0.8, for LMS 0.6 and for ESS 0.2 per 100 000. Nordal and Thoresen reported slightly rising trends of incidence of all USs in Norway (1956–1992): the incidence rate was 1.7 per 100 000 during the latest study period of 1987–1992. The authors concluded that raised rates are mainly explained by the increase in the occurrence of CSs. The timeframe of their incidence analysis is also covered by our study period. Our stable trends in LMS and ESS in Norway are in accordance with the findings of Nordal and Thoresen (1997). Comparing our rates with the incidences reported by Harlow et al., the incidence rate of LMS was only slightly lower in Nordic countries than in the United States in the first five-year study period. The difference in incidence rates of LMS was more notable when Nordic rates were compared with the rates in the black race subgroup of patients (0.99 per 100 000) in the report by Harlow et al. (Harlow et al. 1986).

Trends in incidences of diseases or malignancies can be influenced, for example, by changes in risk factors among the study population, aging of the population and changes in diagnostics. According to NORDCAN, the estimated annual age-standardized incidence rate of cancer of corpus uteri has been shown as a still growing trend of +0.2% in the last 10 years (Engholm et al. 2010a). The use of menopausal hormone therapy increased from the late 1970s until the late 1990s in all Nordic countries, while there was a decrease in menopausal hormone therapy sales in Iceland, Norway, Sweden and Finland from the year 2000 to 2005 (Hemminki et al. 2008) following the publication of the results of the Women's Health Initiative study (Rossouw et al. 2002). Hormone treatment has been associated with a risk of US (Schwartz et al. 1996), and the use of estradiol-progestin menopausal hormone replacement therapy for 5 years or longer has been connected with a two-fold risk of USs (Jaakkola et al. 2011). However, we did not observe any clear changes in the incidence rates

of LMS or ESS in these countries during the study period. Unfortunately, it was not possible to analyze the incidence rates of uterine CS in our study. It would have been interesting, because in the above-mentioned Norwegian study (1956–1992) the incidence of CS increased. The authors speculated that it could have been related to some environmental factors in the etiology of CSs (Nordal and Thoresen 1997).

Diagnostic changes in pathology were introduced for LMS after the revision of WHO classification concerning the female genital organs in 2003 (Tavassoli and Devilee 2003, D'Angelo et al. 2009). It has been suggested that the new criteria have led to a reduction of misdiagnoses of STUMPs and leiomyoma variants such as LMSs (D'Angelo et al. 2009). Nordic trends in incidences of LMSs changed only slightly within the latest study period: in Finland and Denmark incidences decreased and in Iceland and in Norway they increased. This could mean that the new criteria have had a bi-directional influence on diagnostics in pathology – earlier diagnosis of low-grade LMS may have changed to STUMP and STUMP to low-grade LMS in different countries.

It is a well-known fact that the Nordic population is ageing (Statistics Denmark 2010), and one of the risk factors for US, obesity, is becoming more and more common among women. We observed peak incidences of both LMS and ESS around the menopause, in which period of life women may experience weight gain, increases of central adipose tissue and other changes of body composition (Freeman et al. 2010). In the perimenopausal period the imbalance of secreted ovarian hormones and elevated levels of gonadotropins can theoretically be associated with peak incidences of LMS and ESS, much like the hypergonadotropic hypogonadal state is thought to be related to the peak incidence of ovarian cancer (Cramer 1990).

In conclusion, the incidence rates of LMS and ESS showed minor differences between the countries and only modest changes over the study period.

Occupational risks of uterine LMS and ESS in Nordic countries

In Study I, significantly elevated incidence rates of LMS were observed among shoe and leather workers, farmers and teachers. No occupations with an elevated risk of ESS were noticed.

We observed the highest SIR (2.59, 95%CI 1.12–5.11) for LMS among shoe and leather workers. Pukkala et al. also noticed a slightly elevated SIR (1.33, 95%CI 1.12–1.58) in connection with cervical cancer among shoe and leather workers, but no other gynecological cancer site or soft tissue sarcoma has been associated with this occupational group in NOCCA data (Pukkala et al. 2009, Riska et al. 2012). According to NOCCA job exposure matrices

(JEMs), shoe and leather workers are exposed to carcinogenic agents such as benzene, toluene, 1,1,1-trichloroethane, methylene chloride and trichloroethylene (Kauppinen et al. 2009). Cervical cancer has been associated with occupational exposure to agents such as aliphatic, alicyclic, aromatic, and chlorinated hydrocarbon solvents (Weiderpass et al. 2001). Even though the association of LMS with shoe and leather workers may be a chance finding, based on only eight observed cases, occupational exposure to chemicals in the shoe and leather industries has been related to several cancer sites and soft tissue sarcomas (Mikoczy et al. 1996, Lope et al. 2009). Our result may reflect the possibility that occupational exposure among shoe and leather workers could be carcinogenic as regards uterine LMS.

In the current study overpresentation of LMS among farmers is a unique finding compared with other gynecological cancer sites (Pukkala et al. 2009, Riska et al. 2012). In a recent NOCCA study, the risk of primary fallopian tube cancer (SIR 0.68, 95%CI 0.47–0.95) was reported to be significantly and consistently low for women working in farming and was partly explained by the higher parity of female farmers (Riska et al. 2011). Female farmers tend to have more childbirths than other occupational groups (Pukkala 1995, Pukkala et al. 2009). A farmer´s occupation is related to lifestyle factors (low smoking prevalence, low alcohol consumption and highly physically active work) that are inversely associated with several cancer types (Pukkala et al. 2009). An increasing number of full-term pregnancies reduces the risks of endometrial cancer, ovarian cancer and primary fallopian tube cancer (Kvale et al. 1988, Albrektsen et al. 1995, Schwartz et al. 1996, Hinkula et al. 2002, Hinkula et al. 2006, Riska et al. 2007b), but its effect on the risk of US is unclear (Kvale et al. 1988, Schwartz et al. 1991). The mechanism of how pregnancies lower the risk of certain cancers is not understood. In the case of endometrial cancer, it has been thought that progesterone is the key inhibitor of carcinogenesis and a major endometrial tumor suppressor. Progesterone acts though genomic and non-genomic regulation. It promotes apoptosis, cell differentiation and cell cycle arrest and inhibits invasion and inflammation (Yang et al. 2011). Another suggested explanation has been that pregnancy and delivery could mechanically clean possible pre-malignant uterine lining cells (Albrektsen et al. 1995). However, we speculate that these theories may work differently in cases of US that originate from the mesenchymal compartment of the uterus and express both ERs and PRs in different proportions. Furthermore, after several pregnancies, women tend to gain weight, which correlates with higher estrogen levels (Wolfe et al. 1997). Both an overweight condition and estrogen are considered to be potential risk factors of US. We can hypothesize that multiparity or its consequences may increase the risk of uterine LMS in women farmers.

In agricultural work, farmers and farm workers are exposed to animal dander (dust) and several chemicals (Blair and Zahm 1995, Blair and Freeman 2009, Kauppinen et al. 2009). Animal dusts are known causes of respiratory tract irritation and allergy, and organic dusts are thought to represent occupational carcinogenic exposure (Laakkonen et al. 2006). In the Nordic countries, according to a NOCCA JEM, about 90 percent of female farmers are exposed to animal dust, and the level of exposure was 0.01–0.02 mg/m^3 during 1945–1994

(Kauppinen et al. 2009). Weiderpass and co-workers have reported that women exposed to animal dust (furriers and fiber processors) showed a higher risk of endometrial cancer during the study period 1971–1995 in Finland (Weiderpass et al. 2001). Animal dust exposure might be related to the increased risk of LMS observed in women farmers, although the supposed mechanism is unclear.

Although we found an increased risk of LMS among teachers, this association is difficult to explain. In earlier studies this occupation has been reported to be associated with elevated risks of breast, uterine and ovarian cancers (Bernstein et al. 2002, Pukkala et al. 2009). These excess risks could possibly be associated with teachers' health habits rather than occupational exposure.

In conclusion, the overpresentation of LMS in women exposed to leather work and women farmers could be assumed to be multifactorial and this finding has to be considered as a very preliminary one.

Prognostic factors and survival in cases of uterine CS, LMS and ESS

Prognostic factors of US help us to concentrate on appropriate postoperative management and research into better adjuvant therapies. In our study age, stage, tumor size, and parity were proven to have independent influences on overall survival, and stage, tumor size and parity also independently influenced disease-specific survival in multivariate analysis. Many authors have come to the same conclusions as regards these traditional prognostic factors: age (Wolfson et al. 1994, Kokawa et al. 2006, Chan et al. 2008, Kapp et al. 2008, Nemani et al. 2008, Gadducci 2011), stage (Wolfson et al. 1994, Chauveinc et al. 1999, Kokawa et al. 2006, Chan et al. 2008, Kapp et al. 2008, Nemani et al. 2008, Abeler et al. 2009, Gonzalez Bosquet et al. 2010) and tumor size (Wolfson et al. 1994, Nordal and Thoresen 1997, Wu et al. 2006, Abeler et al. 2009, D'Angelo et al. 2011). Tumor size is nowadays included in the new FIGO staging system (2009) of uterine LMS and ESS (Mutch 2009).

Tumor grade has earlier been accepted as a prognostic factor of USs (Nordal et al. 1996, El Husseiny et al. 2002). In Study II, grade was statistically significantly associated with survival in univariate analysis but not in multivariate analysis. Its close association with stage could explain this. We still used the classification of LMS and ESS as low- and high-grade in Study II. Several different grading systems have been used and assessed in connection with USs (Pautier et al. 2000, Sleijfer et al. 2007), but no universally accepted grading system exists. In the WHO´s latest classification for the female genital organs, CS is a high-grade tumor and ESS a low-grade one (Tavassoli and Devilee, 2003). After reclassification there is now no benefit in assessing grade as a prognostic factor for CS and ESS. Although the grading of

LMS is still debated, a high tumor grade has been associated with worse prognosis of LMS patients (Gadducci 2011).

The association between parity and prognosis in patients with USs is unclear, whereas nulliparity is associated with a worse prognosis in patients with endometrial cancer (Albrektsen et al. 2009a). However, in our series survival in all cases of US was negatively affected by increasing parity (up to three deliveries), both in univariate and multivariate analysis. Higher parity among CS patients has been associated both with better survival and higher risks of death and recurrence (Marth et al. 1997, Sagae et al. 2004), or no association at all has been detected (Nordal et al. 1997, Bodner-Adler et al. 2001).

In a Norwegian study of 493 US patients, nulliparity was independently related to a worse prognosis only among patients with ESS (Albrektsen et al. 2009b). The authors have explained the positive effect of pregnancies on the prognosis of ESS by suggesting a possible suppressive effect of progesterone on very early disease, pregnancy-induced alteration in protein content of the uterus or an immunologic mechanism (Marth et al. 1997, Albrektsen et al. 2009b). Our results do not support these hypotheses.

Our survival figures were somewhat better than those of our institution in 1958–1977 (Kahanpaa et al. 1986) and nearly the same as in 1937–1964 (Nieminen and Soderlin 1974). Nieminen et al. found a 5-year survival rate as high as 54.7% (our 5-year overall survival rate was 51%), which could be explained by differences in the proportion of early stages in the study population. As expected, patients with ESS showed the best survival rate, even though the high-grade group (undifferentiated endometrial sarcomas) was included in our study. Our survival rates are comparable to or even better than those in similar studies (Table 7). Our high proportion of stage I diseases (54% of uterine sarcomas), radical primary surgery (lymph node status clarified in 52%) as well as the wide use of first-line therapies (78% of the patients: CT 41%, RT 51%) could to some degree explain our rates, although the role of LND and adjuvant therapies is very controversial (Amant et al. 2009a, Hensley 2011, Sampath, Gaffney 2011). Furthermore, nearly 70% of the cases with recurrent disease were treated by means of different treatment modalities.

Some of the prognostic factors tested failed to reach statistical significance and this might be explained to some extent by the small sample size. We also observed clinically significant results in Study II. For example, the median survival time of LMS patients was 1.6 times longer than among CS patients and the median survival time of patients with US who had adjuvant RT was 2.4 times longer than that of patients without adjuvant RT. Furthermore, patients treated with adjuvant CT had a median survival time that was 8 months longer (72 months versus 64 months).

Our results confirm the status of the traditional prognostic factors of US (age, stage and tumor size) and relatively quite stable survival times in cases of these malignancies over many years. The biological behavior of uterine CS, LMS and ESS could be different that of endometrial

cancer and other gynecological cancers and the association of parity with different subgroups of US still remains an open question.

Prognostic and clinical importance of p53, estrogen receptor-α and progesterone receptor on uterine CS, LMS and ESS

In Study III, we investigated uterine CS, LMS and ESS using a panel of ten IHC markers (Ki-67, p53, CD10, CD44, desmin, SMA, AR, ER-α, PR and c-kit). Both the expression rate (all markers) and the association of the IHC markers (except for AR and c-kit) with survival were assessed.

Mutation of the p53 tumor suppressor gene and overexpression of mutant p53 protein detected by IHC is a relatively frequent phenomenon in gynecological cancers (Berchuck et al. 1994). It has been related to the prognosis, for example, of ovarian malignancies (Ala-Fossi et al. 1997, Lassus et al. 2003). We noticed that the expression rate of the mutant protein p53 in cases of CS and LMS was lower than in earlier reports (Nordal et al. 1998, Gokaslan et al. 2005, Chen and Yang 2008), and most of the ESS samples did not express p53, which is in line with the results of a recent study (D'Angelo et al. 2009). This finding is easily understandable because low-grade ESS usually has a low mitotic rate and on the other hand overexpression of mutated protein p53 is associated with cell proliferation (Tavassoli and Devilee 2003). In accordance with this, the high proportion of low-grade LMSs in our series could explain the low expression rate of p53 in LMS cases. On the other hand, high-grade uterine CS is thought to be the most aggressive subtype of uterine malignancy (Amant et al. 2005, Vaidya et al. 2006) and this could be the reason for the high proportion of CS cases with negative p53. Aberrant p53 staining could be related to the aggressiveness of uterine CS, because both p53 overexpression and total negativity are thought to be strong and independent prognostic factors as regards overall survival in cases of serous ovarian carcinoma (Lassus et al. 2003, Lassus and Butzow 2007). In the present study, a strong survival benefit was associated only with p53-negative cases of LMS: the median survival time was 11 times longer among p53-negative patients than among p53-positive patients (123 months *vs* 11 months, $p = 0.011$). Most earlier studies have shown the similar results, especially in cases of LMS (Blom et al. 1998a, Anderson et al. 2006, Kim et al. 2006, D'Angelo et al. 2009).

In the current study about 40% of cases with LMS and 50% of cases with ESS were positive for ER-α and PR and most cases of CS were ER-α- and PR-negative (77% and 74%). Both ER-α and PR expression in LMS cases were associated with better survival. Our results concerning expression rates of ER-α and PR in all US subgroups mostly concur with the results of earlier studies (Ansink et al. 1997, Leitao et al. 2004, Leitao et al. 2012). However, both lower and higher expression rates of ER-α have been published in connection with

patients with USs (Akhan et al. 2005, Kir et al. 2005, Ioffe et al. 2009), which could be related to differences in the study population and IHC methods.

Many authors have agreed on the prognostic clinical significance of hormone receptor positivity among patients with LMS (Raspollini et al. 2003, Leitao et al. 2004, Akhan et al. 2005, Ioffe et al. 2009, Leitao et al. 2012). The same issue has earlier been established in endometrial carcinoma and this phenomenon has in general been associated with the tumors derived from hormone receptor-positive tissue (Uharcek 2008). The significance of hormone receptor status has even been extended to concern all cases of US in a recent report (Ioffe et al. 2009). We can also speculate about clinically significant outcomes in cases of ESS and CS: all of the ESS patients with positive ER-α and PRA status were alive at the cut-off point for survival analysis in our study (these patients were alive at 107, 152, 177 and 184 months after ESS diagnosis), and the median survival time of CS patients with an ER-α-positive tumors was 102 months, compared with only 20 months among ER-α-negative patients. Expression of ER-α has been associated with a reduced risk of death, and, in contrast, overexpression of ER-β with advanced stage of disease among CS patients (Huang et al. 2007, Huang et al. 2009).

The hormone receptor status of malignancies may have an effect on prognosis and it can also be used in deciding on therapies. Hormone therapy, especially with progestins or aromatase inhibitors, has been gradually accepted as a standard of care in cases of ESS and it should be kept in mind in cases of ER-/PR-positive LMS (Amant et al. 2009a, Sjoquist et al. 2011).

According to our results, IHC testing of ER-α and PR in cases of LMS and ESS can be recommended. On a larger scale, hormone therapy could be offered as one of the options for patients with recurrent, or even primary, hormone receptor-positive uterine sarcomas.

Second primary cancer after first primary uterine sarcoma

The present multicenter study showed that women with primary USs had a 26% increased risk of developing a new primary cancer compared with the general population. We observed excesses in cancers of the mouth and pharynx, colorectum, lung, breast, urinary bladder, kidney, thyroid gland, and soft tissue sarcomas. The only other study (to our knowledge) published on second primary cancers after first primary US showed comparable results (Curtis et al. 1985).

The major etiologic groups of second malignancies are treatment-related, syndromic, and malignancies with shared etiologic factors (Travis et al. 2006), but strict surveillance after any first primary cancer should not be forgotten (Boice et al. 1985b). In this study, most of the kidney and thyroid cancers were detected within the first few years after diagnosis of US, when frequent monitoring after malignancy is usual and a surveillance effect or bias is most

likely an explanation for the elevated risks of these two cancer types after primary US. The increased incidence of colorectal and bladder cancers could be partly explained by the possible late effects of radiotherapy. Even though surgery is the most common treatment modality for any type of US, adjuvant radio- or chemotherapy is still used to different degrees (Gadducci et al. 2007, Hensley 2011, Sampath and Gaffney 2011). The probability of developing an independent second primary malignancy after radiotherapy increases with time (Welte et al. 2010), and both colorectal cancer and urinary bladder cancer have been linked to medical radiation (El Ghissassi et al. 2009). However, the elevated risk of bladder cancer could also be associated with chemotherapy. The risk of chemotherapy-induced second primary bladder cancers has been related to cyclophosphamide (Grosse et al. 2009), which has been used in the treatment of US during this study period (Muss et al. 1985, Benoit et al. 2005).

Smoking is a well-known risk factor for cancers of lung, mouth, pharynx, bladder and kidney (Dreyer et al. 1997). In the present study, we detected elevated risks after first primary US at all these cancer sites. However, cigarette smoking has been associated with a reduced risk of endometrial cancer, and earlier reports of second primary malignancies among patients with endometrial cancer have confirmed a negative and also a bidirectional association of smoking-related malignancies (Hemminki et al. 2003, Zhou et al. 2008, Brown et al. 2010). The mechanism behind the protective effect of smoking on endometrial cancer is that tobacco smokers tend to have less body fat and lower estrogen levels (Zhou et al. 2008). The only study on smoking and US showed odds ratios of 0.6 (95%CI 0.3–1.1) for LMS and 0.5 (95%CI 0.1–1.2) for ESS among patients who had ever smoked (Schwartz et al. 1996). Although our results contrast with those reported by Schwartz and coworkers, we can still speculate that smoking might have an unknown carcinogenic effect on US.

In our study, patients with US had an elevated risk of breast cancer. The relative risk was highest in women of 60 years of age and over at the time of diagnosis of US. Breast cancer has been linked to hormone treatment (Rossow et al. 2002), and some hormonal agents are thought to be associated with the risk of US (Schwartz et al. 1996, Wickerham et al. 2002, Arenas et al. 2006). In a recent study elevated risks of US were reported among postmenopausal women who used estradiol-progestin for five or more years (Jaakkola et al. 2011). This is plausible, since estrogen, progesterone and androgen receptors are expressed in USs to different degrees (Ansink et al. 1997, Leitao et al. 2004, Akhan et al. 2005, Kir et al. 2005, Ioffe et al. 2009, Leitao et. al 2012). The association between these malignancies could be explained by a shared hormonal etiology. Furthermore, obesity is one of the few known risk factors of US and also a risk factor of postmenopausal breast cancer, colorectal and renal cancers, all of which were increased among the US patients. Hence, shared risk factor etiology is another explanation for these findings.

To the best of our knowledge, this is the largest US patient cohort ever collected for this kind of study. We were able to observe statistically significant associations between US and certain cancer types. However, the rarity of USs and the lack of individual data on the patients

prevented us from assessing the proportion of different causes for the excess risks of second primary malignancies. The results of the present study emphasize the need for long-term caution as regards new malignancies among women with US.

Implications for future research

Our results emphasize the rareness of USs and the lack of information on possible etiological and risk factors and treatment modalities. Future research should be focused on multinational (for example Nordic) cooperation linking national registries of birth (association with parity), medical reimbursement (hormone replacement therapy, use of levonorgestrel-releasing IUDs) and hospital discharge (anamnestic factors: body mass index, smoking habits etc. and earlier diseases) to databases such as NORDCAN and NOCCA. More efforts should be made to conduct prospective trials to assess different therapy strategies in cases of US. Since it is difficult to find enough material for such studies in gynecologic oncology centers in Finland, more extensive cooperation with international clinical trial organizations such as NSGO, AGO, ENGOT etc. would be needed. Because of the variable biological behavior of USs, subgroup analysis has an essential role in large, multinational studies. The aim could be assessment of different therapy strategies in connection with US – LMS, ESS, adenosarcoma and UES. It would be particularly interesting to study progestins, mifepristone (Koivisto-Korander et al. 2007), and aromatase inhibitors in cases of recurrence and in adjuvant settings alone or with chemotherapy among patients with LMS and ESS. New biologic agents such as tyrosine kinase inhibitors should also be evaluated further in the treatment of USs.

CONCLUSIONS

On the basis of the present work the following conclusions can be drawn

1. During the study period (1978–2007), the incidences of LMS and ESS showed slight differences between the Nordic countries concerned and only minor changes in incidence over time. In our study the age-specific incidences of LMS and ESS increased up to the age groups around menopause (45–59 years), but decreased after the age of 60 in cases of LMS. There were some differences in uterine sarcoma incidences related to occupational factors (leather work) which merit further investigation.

2. The disease-specific and overall survival rates were slightly better than in nearly all previous similar studies of uterine sarcomas. Stage, age, tumor size and parity were found to be the most important prognostic factors as regards survival. The association between parity and USs should be further studied.

3. The expression of p53, ER-α and PR in uterine LMS may give prognostic information concerning the behavior of the disease and IHC testing for ER-α and PR in cases of LMS is recommended. Patients with ESS might also benefit from testing for hormone receptor expression. Patients with LMS and ESS should also have the option of hormone therapy in adjuvant and recurrent settings.

4. Uterine sarcoma survivors had a 26% increased risk of developing a second primary cancer, such as cancers of the mouth and pharynx, colorectum, lung, breast, urinary bladder, kidney, thyroid gland, and soft tissue sarcomas. Colorectal and urinary bladder cancer may be related to the use of pelvic radiotherapy or chemotherapy (urinary bladder only). The other associations are more difficult to explain.

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